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18

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ACC ANNUAL MEETING DATES:
MARCH 6–9, 1978, ANAHEIM, CALIFORNIA

Tenth Bethesda Conference: Optimal Electrocardiography

Electrocardiographic Estimate of Myocardial Infarct Size

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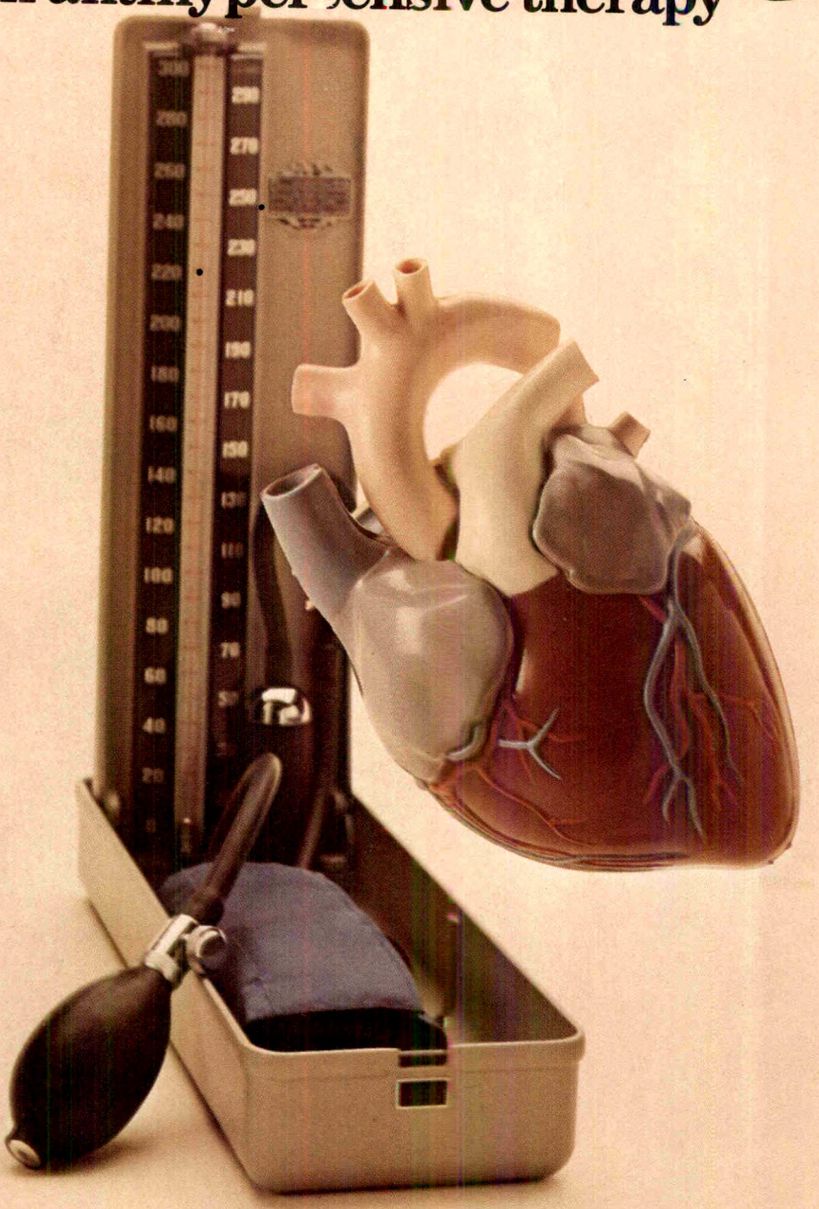
A Dual Challenge

in antihypertensive therapy



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without compromising existing cardiac output

addendum

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It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

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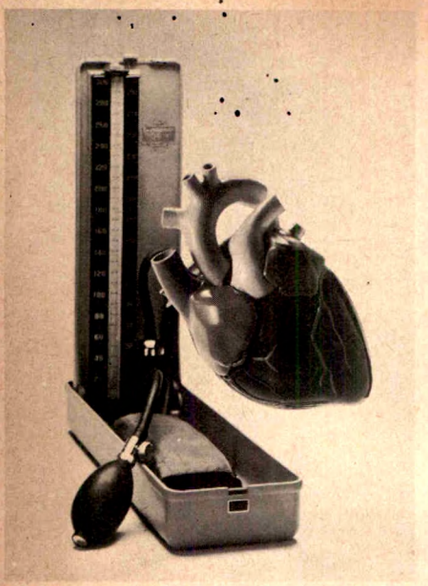
For a brief summary of prescribing information, please see following page.



in hypertension

ALDOMET®

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helps lower blood pressure effectively... usually with no direct effect on cardiac function– cardiac output is usually maintained

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism; to increase diuresis in patients resistant to other diuretics. Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy when edema is due to pathological causes (see Warnings).

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the [illegible]. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance; low-salt syndrome (with low salt intake), reversible mild nitrogen retention; decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

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Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

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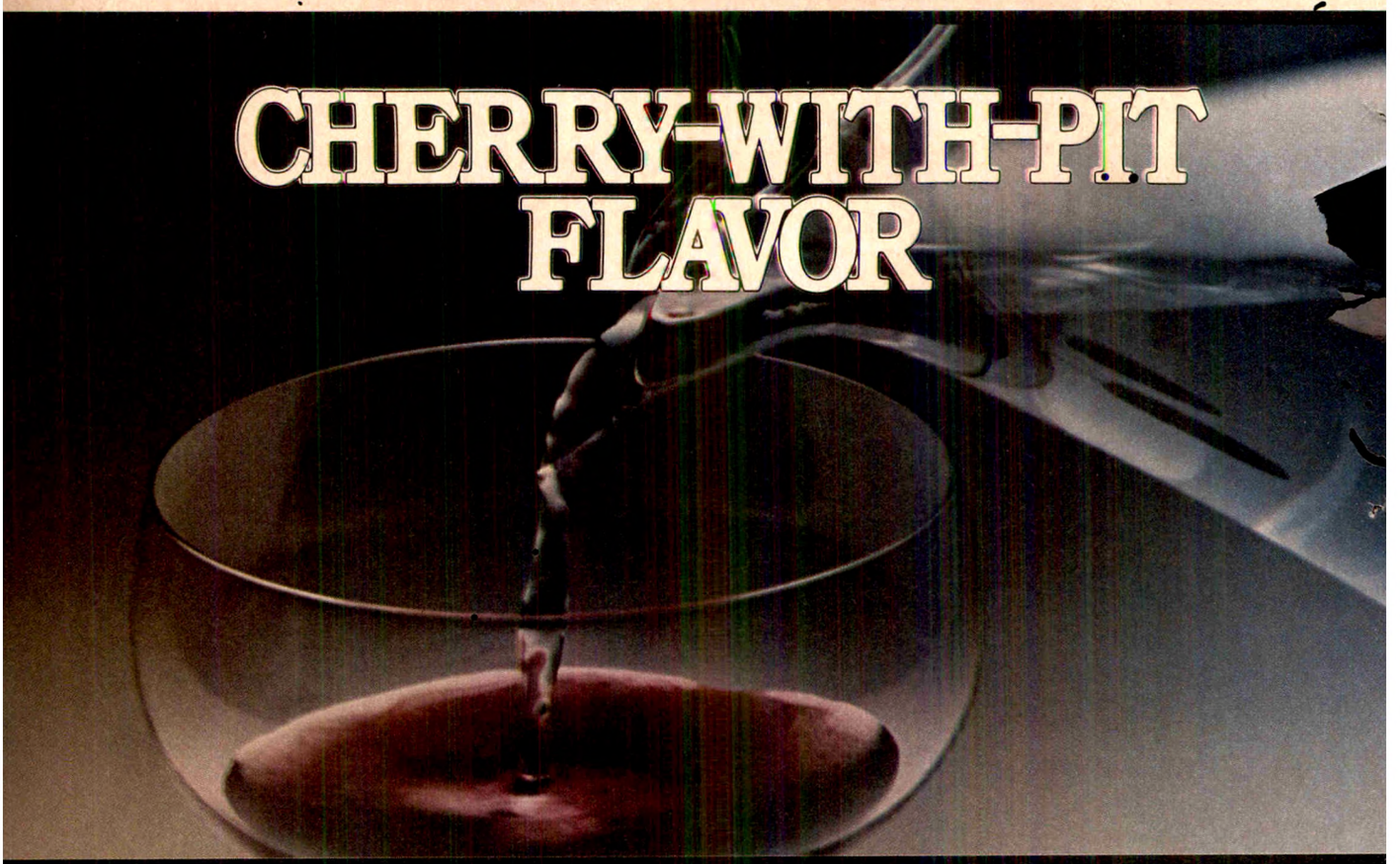

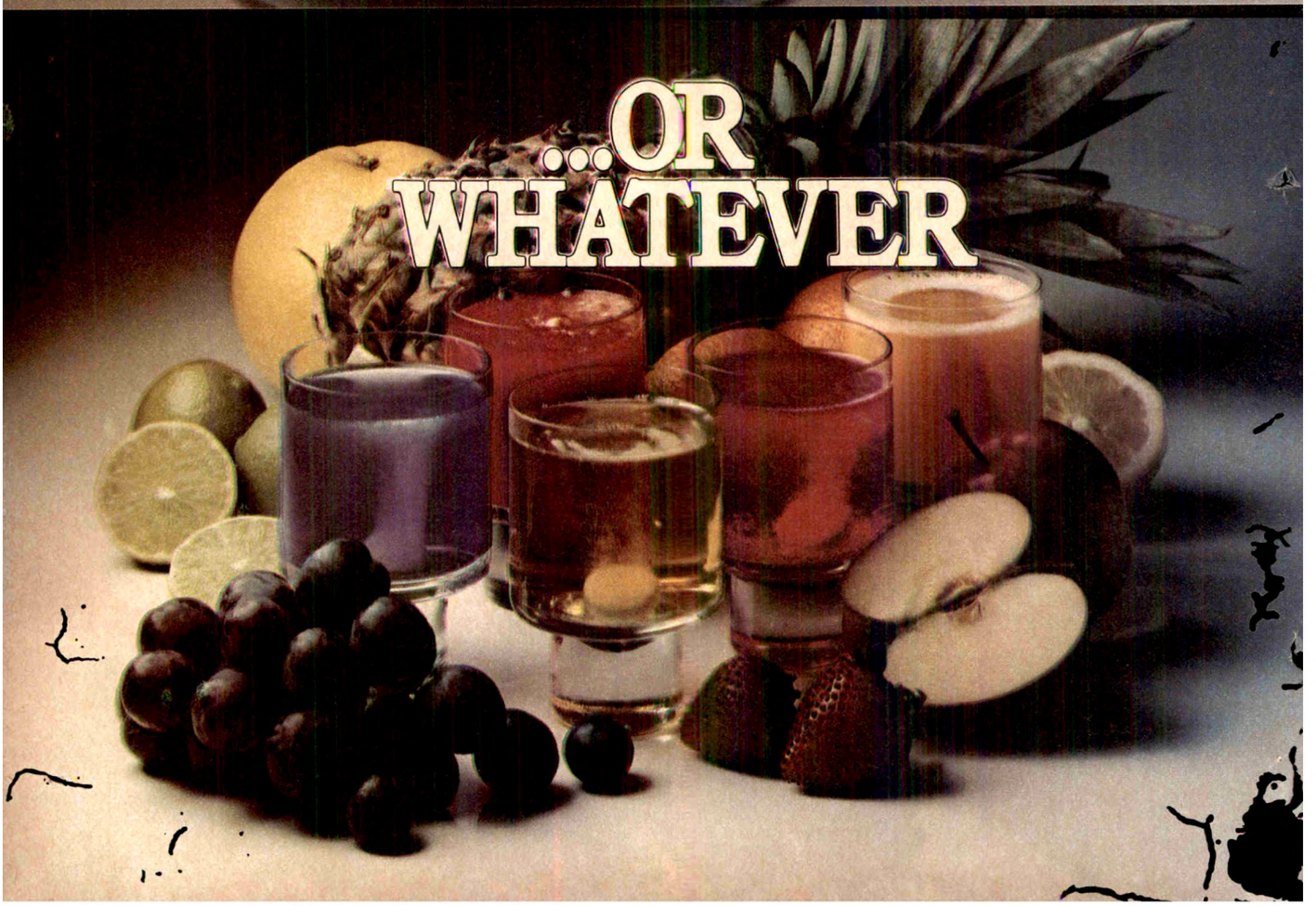

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Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable cherry-with-pit flavored vehicle, alcohol 1%.

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Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g.

Or whatever flavor your patients like . . . because the taste of KLORVESS® Effervescent Tablets is determined by what they're mixed with. The subtle mixer.

Convenience in therapeutic doses.
Both forms of KLORVESS offer 20 mEq of potassium and chloride in each dose. There is no need to prescribe several slow-release tablets per dose or space dosage administration beyond the patient's normal routine. Prescribe KLORVESS Liquid or KLORVESS Effervescent Tablets . . . for potassium supplement therapy that offers good taste and convenience at therapeutic dosages.

Description: Klorvess Effervescent Tablets: Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g. Dissolution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 100 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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BD--B

JANUARY 1978

The American Journal of CARDIOLOGY®

VOLUME 41

NUMBER 1

CONTENTS

CLINICAL STUDIES

1 **Approach to the Estimation of Myocardial Infarct Size by Analysis of Precordial S-T Segment and R Wave Maps**

HARTMUT HENNING, THORDUR HARDARSON, GARY FRANCIS, ROBERT A. O'ROURKE, WILLIAM RYAN and JOHN ROSS, Jr.

Electrocardiographic mapping of the precordial S-T segment and R wave in 14 patients with uncomplicated acute anterior transmural myocardial infarction showed good correlation with infarct size as estimated from serial creatine kinase (CK) curves. Similar results were found prospectively in 10 additional patients. On the basis of these results, the investigators conclude that in selected patients CK-determined infarct size can be directly related to the initial height of S-T segment elevations and the early rate of R wave decline and inversely related to late ΣR values. However, the potential significance of these correlations for early prediction of infarct size from precordial electrocardiographic maps and for assessment of the effects of therapeutic interventions will require further exploration in a more diverse population.

9 **Computerized Orthogonal Electrocardiogram: Relation of QRS Forces to Left Ventricular Ejection Fraction**

MARTIN G. GOTTWIK, ALFRED F. PARISI, JOSEPH ASKENAZI and DONALD McCAUGHAN

This study in 52 consecutive patients being evaluated with cardiac catheterization for chest pain confirms that changes of the QRS complex may be used as an index of left ventricular function. The orthogonal ΣR value (Rx + Ry + Qz) in these patients proved to be a good indicator of left ventricular function, more accurate in the presence of anterior and lateral wall damage than in inferior infarction. A significant correlation was obtained between the voltages of the R waves in the X, Y and Z leads and of the Q waves in lead Z (Qz) as well as total amplitude Qx + Rx, Qy + Ry and ejection fraction ($P < 0.01$). ΣR contained important information of practical use in the precatheterization evaluation of patients with chest pain and follow-up evaluation of patients with myocardial infarction.

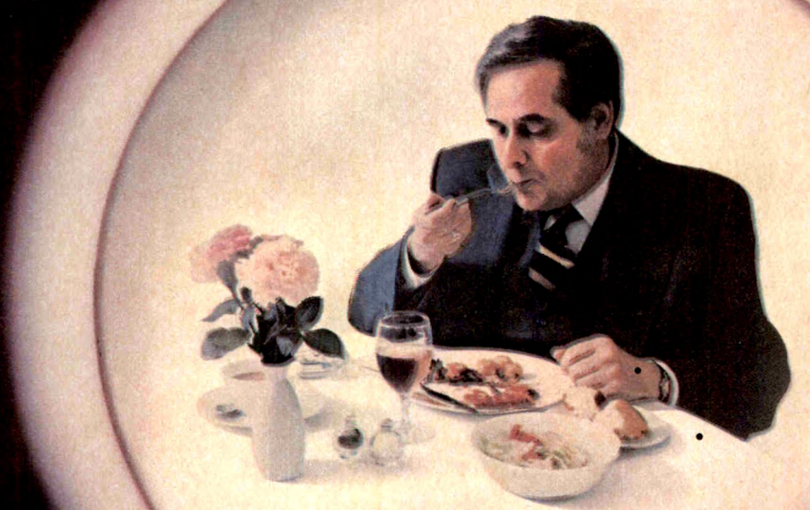
14 **Effects of Postextrasystolic Potentiation on Systolic Time Intervals**

NARASIMHAN RANGANATHAN, VAHE SIVACIYAN and ROBERT CHISHOLM

Measurement of changes in systolic time intervals associated with postextrasystolic potentiation in 48 patients is of value as a noninvasive method to assess resting left ventricular function. Postectopic potentiation caused a decrease in preejection period/left ventricular ejection time (PEP/LVET) ratio, the greatest occurring in beats where the differ-

Continued on page A14

IN PREDICTABLE ANGINA*



...during the postprandial period

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

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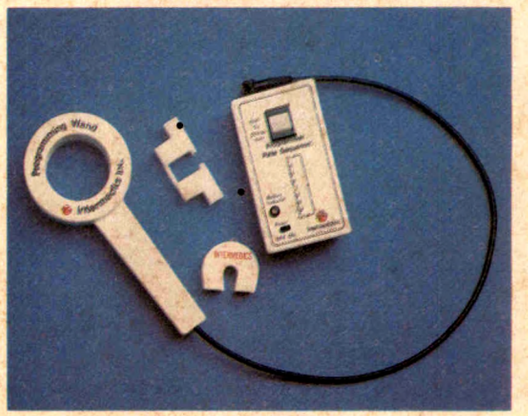

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ence in compensatory pause and coupling interval exceeded 40 percent. Marked shortening of ejection time with minimal shortening of preejection period occurred in patients with normal ventricular function. Marked shortening of preejection period and minimal shortening of ejection time were found in patients with severe left ventricular dysfunction. The probable mechanisms of postextrasystolic potentiation effects on systolic time intervals appear to be related to an increased mean systolic ejection rate accompanied by an increase in the rate of rise of intraventricular pressure (dP/dt).

23 The U Wave and Aberrant Intraventricular Conduction. Further Evidence for the Purkinje Repolarization Theory on Genesis of the U Wave

YOSHIO WATANABE and HITOSHI TODA

Correlating the incidence of aberrancy of atrial premature systoles with the timing of the U wave and other measurements in 126 electrocardiograms selected from 6,000 records, this study concludes that the U wave most likely represents phase 3 repolarization of the Purkinje system, and propagation of supraventricular impulses during this period is the cause of aberrant ventricular conduction. The Purkinje repolarization theory offers plausible explanations for at least several clinical electrocardiographic findings related to the U wave, although the validity of this concept still rests on more direct experimental studies to be carried out in the future.

32 Valve Origin of the Aortic Incisura

HANI N. SABBAH and PAUL D. STEIN

Observations in 66 patients and additional in vitro studies with high speed cinematography of a stented normal porcine valve indicate that the occurrence and magnitude of the incisura of the central aortic pressure depend upon the functional state of the aortic valve rather than upon the distension and rebound of the aortic walls. In the presence of a normal or diseased aortic valve the aortic incisura is produced primarily by valve distension or recoil. This mechanism explains satisfactorily the variations of the magnitude of the aortic incisura in various aortic valve diseases. A prominent aortic incisura implies that the aortic valve is normally distensible; a reduced amplitude implies malfunction of the aortic valve; and an absent or reduced aortic incisura implies aortic valve disease.

39 Myocardial Scintigraphy With Technetium-99m Pyrophosphate During the Early Phase of Acute Infarction

B. LEONARD HOLMAN, MICHAEL LESCH and JOSEPH S. ALPERT

Thirty-one patients admitted to a coronary care unit with prolonged ischemic pain underwent myocardial scintigraphy with technetium-99m pyrophosphate within 4 to 8 hours and again 24 hours after the onset of symptoms. Increased focal myocardial uptake was demonstrated on early myocardial scintigraphy in all 15 patients with documented acute myocardial infarction but in only 2 of 16 patients with unstable angina pectoris. Three of four patients with normal early scintigrams had massive transmural myocardial infarction. This study suggests that technetium-99m pyrophosphate scintigraphy can detect acute myocardial infarction as early as 4 hours after the onset of symptoms although the sensitivity rate (73 percent) is less than that at 24 hours. Infarct scintigraphy may estimate infarct size in most cases within 8 hours of symptoms, but technetium-99m pyrophosphate uptake may not reflect the degree of necrosis within the borders of the infarct.

Continued on page A18

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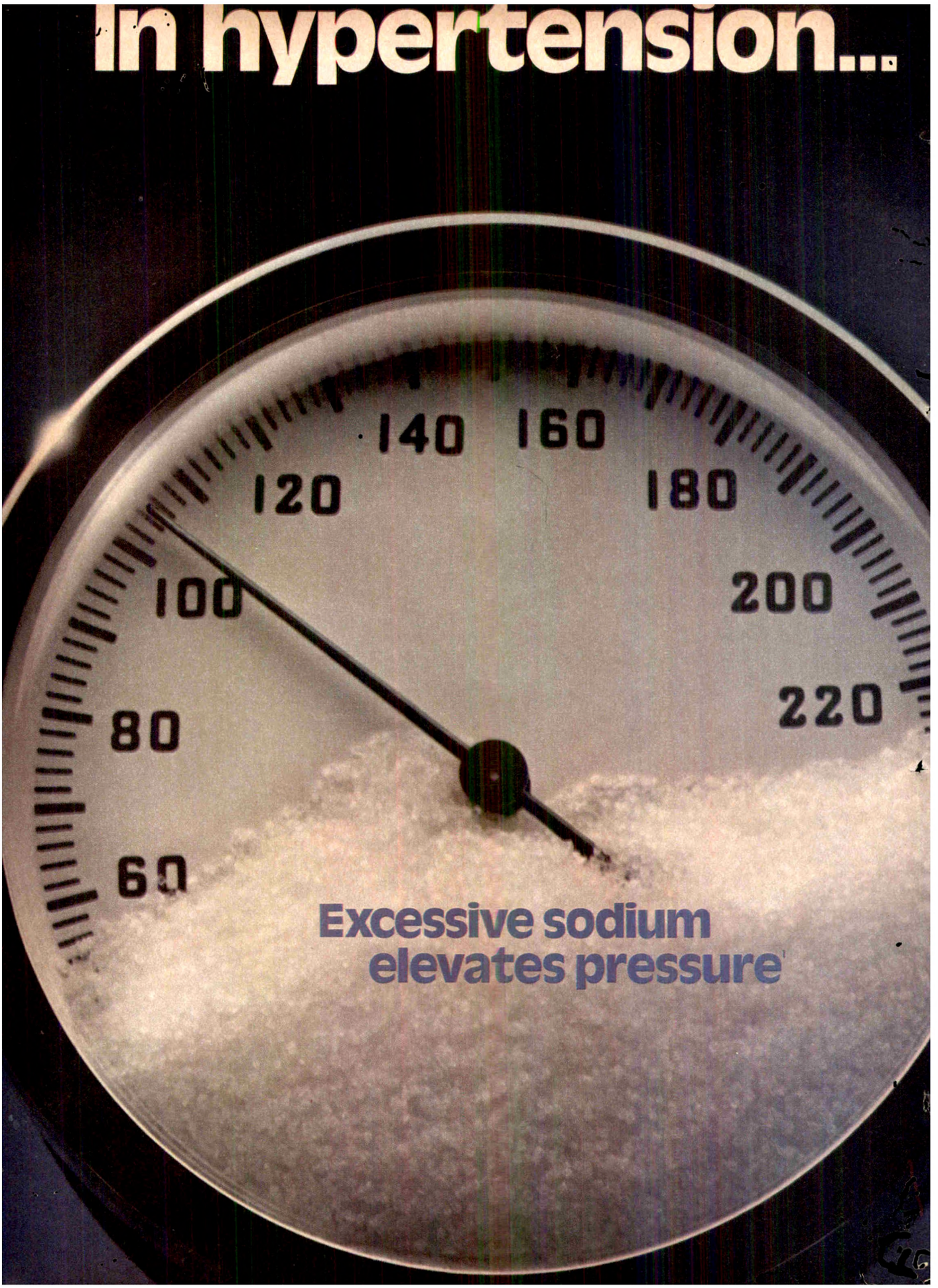
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Blocks sodium retention longer

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Diuretics reduce blood pressure by blocking sodium retention to lower "effective" volume. But, the body's renal compensatory mechanisms are mobilized to promote sodium conservation, expand "effective" volume and reelevate blood pressure. Sustained control of "effective" volume is therefore essential to treatment. Hygroton blocks sodium retention longer than any other diuretic available.

As baseline diuretic in step-2 therapy

Reduced blood pressure resulting from the use of step-2 agents (reserpine, methyldopa, propranolol) may cause compensatory sodium retention, secondary volume expansion and, eventually, reelevation of blood pressure. For this reason, the National Task Force[2] recommends the use of diuretics as baseline agents with step-2 therapy. Hygroton is an "ideal" choice because of its sustained blockade of sodium retention, dosage simplicity and enhanced patient compliance.

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Provides smooth, sustained control

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

References:

1. Laragh, J.H. et al.: Vasoconstriction - volume analysis for understanding and treating hypertension: The use of renin and aldosterone profiles, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, pp. 824-825. **2.** Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: A Cooperative Study, JAMA 237:255, January 17, 1977.

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CONTENTS

43 Thallium-201 Myocardial Perfusion Scintigraphy for the Clinical Clarification of Normal, Abnormal and Equivocal Electrocardiographic Stress Tests

ELIAS H. BOTVINICK, MICHAEL R. TARADASH, DAVID M. SHAMES and WILLIAM W. PARMLEY

This careful study of 65 patients shows thallium-201 relative myocardial perfusion scintigraphy was more sensitive, specific and accurate than stress electrocardiography to diagnose significant coronary arterial lesions in patients with isoelectric S-T segments at rest and even in the presence of a depressed S-T segment at rest. Scintigraphic defects corresponded well with the distribution of coronary arterial lesions as demonstrated on angiography. The stress-induced scintigraphic abnormalities largely reflect perfusion changes whereas stress-induced electrocardiographic changes reflect hypoxic, metabolic and electrophysiologic alterations arising from changes in perfusion. The presence of both an abnormal stress scintigram and an abnormal stress electrocardiogram guaranteed the presence of significant coronary disease in these subjects.

52 Hemodynamics at Rest and During Supine and Sitting Bicycle Exercise in Normal Subjects

UDHO THADANI and JOHN O. PARKER

These bicycle exercise studies in 10 normal untrained subjects show the hemodynamic profile differs in the supine and sitting postures at rest and during exercise. At rest the values for heart rate were higher and the values for cardiac index, stroke index, left ventricular stroke work index, mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure were lower in the sitting position. During both supine and sitting exercise left ventricular end-diastolic pressure, cardiac index, stroke index and left ventricular stroke work index increased significantly from the resting values. The good correlation found between left ventricular end-diastolic pressure and pulmonary capillary wedge pressure at rest and during exercise in the two postures suggests it should be possible to explore left ventricular hemodynamics in the upright posture using the flotation catheter technique, which is a safer procedure than obtaining direct left ventricular pressures.

60 Abnormal Platelet Survival Time in Men With Myocardial Infarction and Normal Coronary Arteriogram

PETER STEELE, JOSEPH RAINWATER and ROBERT VOGEL

Platelet survival time (using chromium-51 labeling) was shortened in eight men with an acute transmural myocardial infarction and a subsequent normal coronary arteriogram. Three patients had recurrent venous thromboembolism and one had had iliofemoral arterial thromboembolism. Platelet survival time was also shortened in 11 of 16 age-matched men with transmural infarction and arteriographic evidence of coronary obstructive disease. These data suggest that coronary arterial thrombosis may be responsible for the myocardial infarction in patients with this complication and a normal coronary arteriogram. Presumably the coronary thrombus completely recanalized by the time of coronary angiography.

EXPERIMENTAL STUDIES

63 Effects of Ionophore RO 2-2985 (X537A) on Conscious Dogs in Experimentally Induced Hemorrhagic Hypotension. Mortality, Systemic Pressure and Renal and Coronary Blood Flow

HENRY G. HANLEY, JULIE A. SWAIN, CRAIG J. HARTLEY, ROBERT M. LEWIS and ARNOLD SCHWARTZ

RO 2-2985, a potent inotropic agent, increases left ventricular pressure and coronary and renal blood flow in conscious dogs. In 18 conscious unsedated chronically instrumented dogs this drug decreased mortality and increased

Continued on page A20

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blood flow in the coronary and renal beds during hemorrhage-induced hypotension. The mechanism by which RO 2-2985 produces these hemodynamic effects is not known although other studies indicate that this drug causes a translocation of large volumes of blood to the central circulation with a decrease in total body venous compliance. It is possible that the combined effects of inotropic stimulation and increased central blood volume are responsible for the results in this study. The striking decrease in mortality and the beneficial hemodynamic effects suggest that this type of chemical agent or a derivative of it may be clinically useful in combination with volume replacement in the therapy of acute hemorrhagic hypotension.

PEDIATRIC CARDIOLOGY

69 Bruce Treadmill Test in Children: Normal Values in a Clinic Population

GORDON R. CUMMING, DAYLE EVERATT and LAVERNE HASTMAN

In 327 children with innocent heart murmurs the Bruce treadmill exercise protocol proved to be highly suitable for the clinical exercise testing of children aged 4 years and older. Mean endurance time in boys increased from 10.4 minutes at age 4 to 5 years, to 14.1 minutes at age 13 to 15 years, and in girls, increased from 9.5 minutes at age 4 to 5 years to 12.3 minutes at age 10 to 12 years. Mean maximal heart rate ranged from 193 to 206 beats/min. For clinical purposes endurance time alone is a satisfactory indicator of exercise performance. The same protocol was used for all ages and permits the collection of longitudinal data on growing children. In contrast to the bicycle ergometer, this method avoids calibration problems and the need to have a large number of work loads based on body weight. No prior experience or practice by the patient is needed. Injury and fear of performing on the treadmill are minor issues because the belt speed is slow.

76 Surgical Significance of the Coronary Arterial Anatomy in Truncus Arteriosus Communis

KENNETH R. ANDERSON, DWIGHT C. McGOON and J. T. LIE

Surgical injury to a major coronary artery was identified in 2 of 30 hearts of patients with truncus arteriosus communis who died in the early postoperative period. In two other cases similar arteries of moderate size were obliterated by sutures attaching the conduit to the right ventriculotomy and in all cases some much smaller vessels were by necessity compromised. At special risk in surgical procedures utilizing a conduit anastomosed to a right ventriculotomy are large branches of the right coronary artery crossing the upper anterior surface of the right ventricle to supply the anterobasal surface of both ventricles and the upper part of the interventricular septum. Special care and preoperative documentation of the coronary arteries, particularly the right coronary artery, with selective coronary angiography may be indicated in these cases.

REPORTS ON THERAPY

82 Effects of Long-Term Oral Administration of Isosorbide Dinitrate on the Antianginal Response to Nitroglycerin. Absence of Nitrate Cross-Tolerance and Self-Tolerance Shown by Exercise Testing

GARRETT LEE, DEAN T. MASON and ANTHONY N. DeMARIA

This investigation indicates that long-term (1 month) oral administration of large doses of long-acting isosorbide dinitrate not only achieves therapeutic efficiency without evidence of self-tolerance but also does not cause cross-toler-

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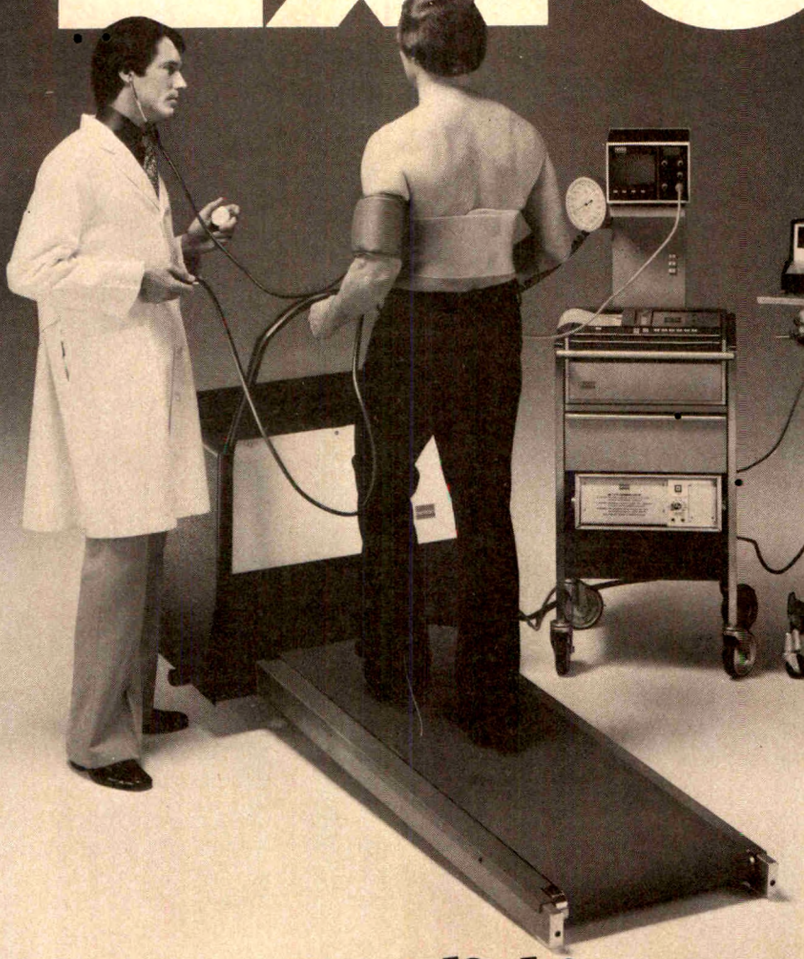

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ance to the antianginal action of sublingually administered nitroglycerin. Maximal duration of exercise, derived index of oxygen consumption, heart rate-blood pressure product and S-T segment depression after nitroglycerin were identical before and after such long administration of the long-acting nitrate preparation. The ability to achieve equivalent improvements in exercise performance before and 1 month after isosorbide dinitrate therapy supports these conclusions.

88 **Effects of Ouabain on Coronary and Systemic Vascular Resistance and Myocardial Oxygen Consumption in Patients Without Heart Failure**

HENRY DeMOTS, SHAHBUDIN H. RAHIMTOOLA, JOHN H. McANULTY and GEORGE A. PORTER

Rapid intravenous administration of ouabain in patients without heart failure produced systemic and coronary arteriolar constriction that may lead to clinical deterioration. Coronary vascular resistance increased 13.4 ± 5.2 percent after a 10 second infusion but did not change during or after a 15 minute infusion. Thirty minutes after ouabain administration mean arterial pressure had returned to control levels but myocardial oxygen consumption remained increased, indicating that ouabain produces a net increase in myocardial oxygen demand in patients without heart failure. These adverse effects can be avoided by slower delivery of the drug. It appears unwise to give digitalis rapidly to a patient with cardiogenic shock when vasoconstriction may be avoided by a slower infusion. The possible deleterious effects of glycosides in myocardial infarction may be more closely related to the vasoconstrictive properties of digitalis than to changes in myocardial oxygen consumption.

94 **Termination of Ventricular Tachycardia With Bursts of Rapid Ventricular Pacing**

JOHN D. FISHER, RAHUL MEHRA and SEYMOUR FURMAN

Bursts of rapid ventricular pacing proved an effective rapid pleasant alternative to repeated direct current cardioversion and a useful tool during electrophysiologic testing in patients with recurrent ventricular tachycardia. Used during 573 episodes of ventricular tachycardia in 23 patients, it terminated 512 episodes (89 percent) with burst rates averaging 56 beats/min above the ventricular tachycardia rate for 5 to 10 captures. A unipolar, low output implantable pacemaker delivering bursts of rapid ventricular pacing proved useful at home in two patients with episodic ventricular tachycardia. For many patients bursts of rapid ventricular pacing have the advantages of easy application, predictable effectiveness and apparent benignity.

CASE REPORTS

103 **Aortic Root Dissection Complicating Coronary Bypass Surgery**

W. JAY NICHOLSON, I. SYLVIA CRAWLEY, R. BRUCE LOGUE, EDWARD R. DORNEY, B. WOODFIN COBBS and CHARLES R. HATCHER, Jr.

Successful surgical correction of aortic root dissection after aortocoronary bypass surgery in two of four patients emphasizes the need to diagnose and treat this potentially fatal complication early. All four patients had long-standing severe hypertensive cardiovascular disease or severe generalized atherosclerotic disease, or both. Patients with dissecting aneurysm may present, as these subjects did, with evidence of aortic regurgitation, cardiac tamponade or severe chest pain, characteristically on the 6th to 8th postoperative day. Awareness of this complication can provide the opportunity for diagnostic aortography and prompt surgical correction. The finding of dilatation of the ascending aorta, congestive heart failure or aortic regurgitation of new onset, alone or in combination, should alert the physician to the occurrence of this complication.

Continued on page A24

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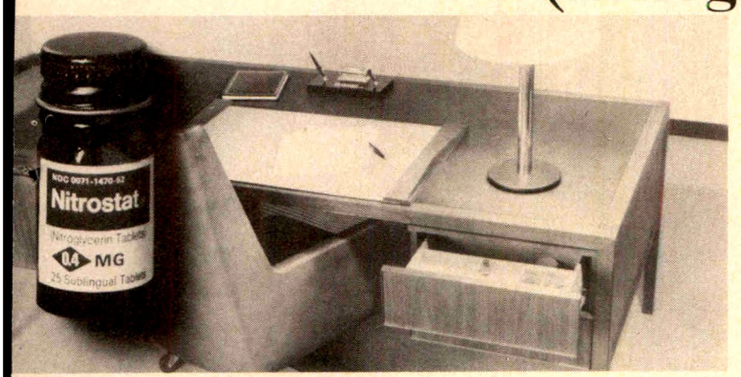

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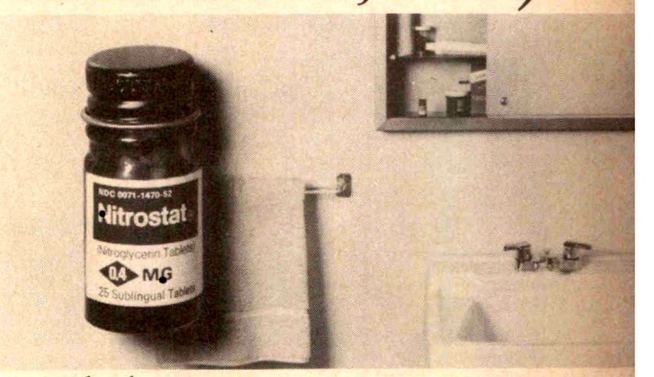

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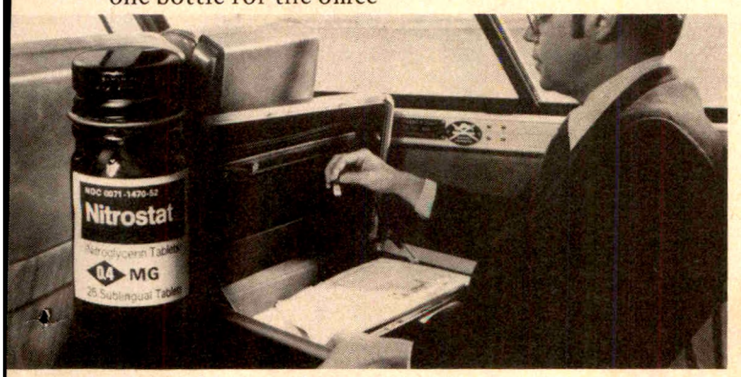

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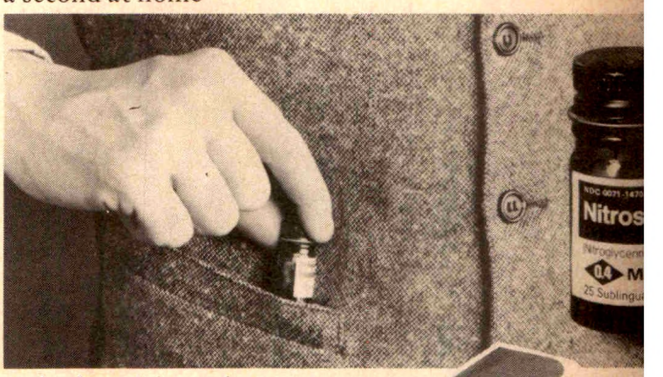

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PAUL D. STEIN and HANI N. SABBAH

BETHESDA CONFERENCE REPORT: OPTIMAL ELECTROCARDIOGRAPHY

Although electrocardiography has firmly established its value in helping to understand better the biologic processes of the heart and to sharpen the diagnosis of cardiac structure and function, the rather mundane but important problems of electrocardiography, such as standardization, record quality, cost effectiveness, and the more fascinating areas of computer analysis, clinical applications and future goals and objectives cannot be overlooked. This Bethesda report discusses these issues fully and the recommendations undoubtedly will become future guidelines for physicians, administrators and government officials. The report of Task Force IV on "Use of Electrocardiograms in Practice" contains useful suggestions on assessing competence and education in electrocardiography. Task Force VI predicts that future electrocardiography will be directed toward surface potentials, cardiac conduction and arrhythmias.

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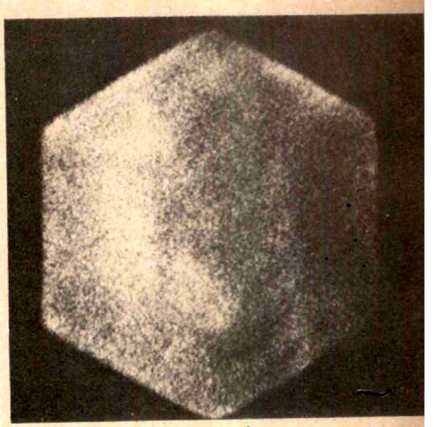
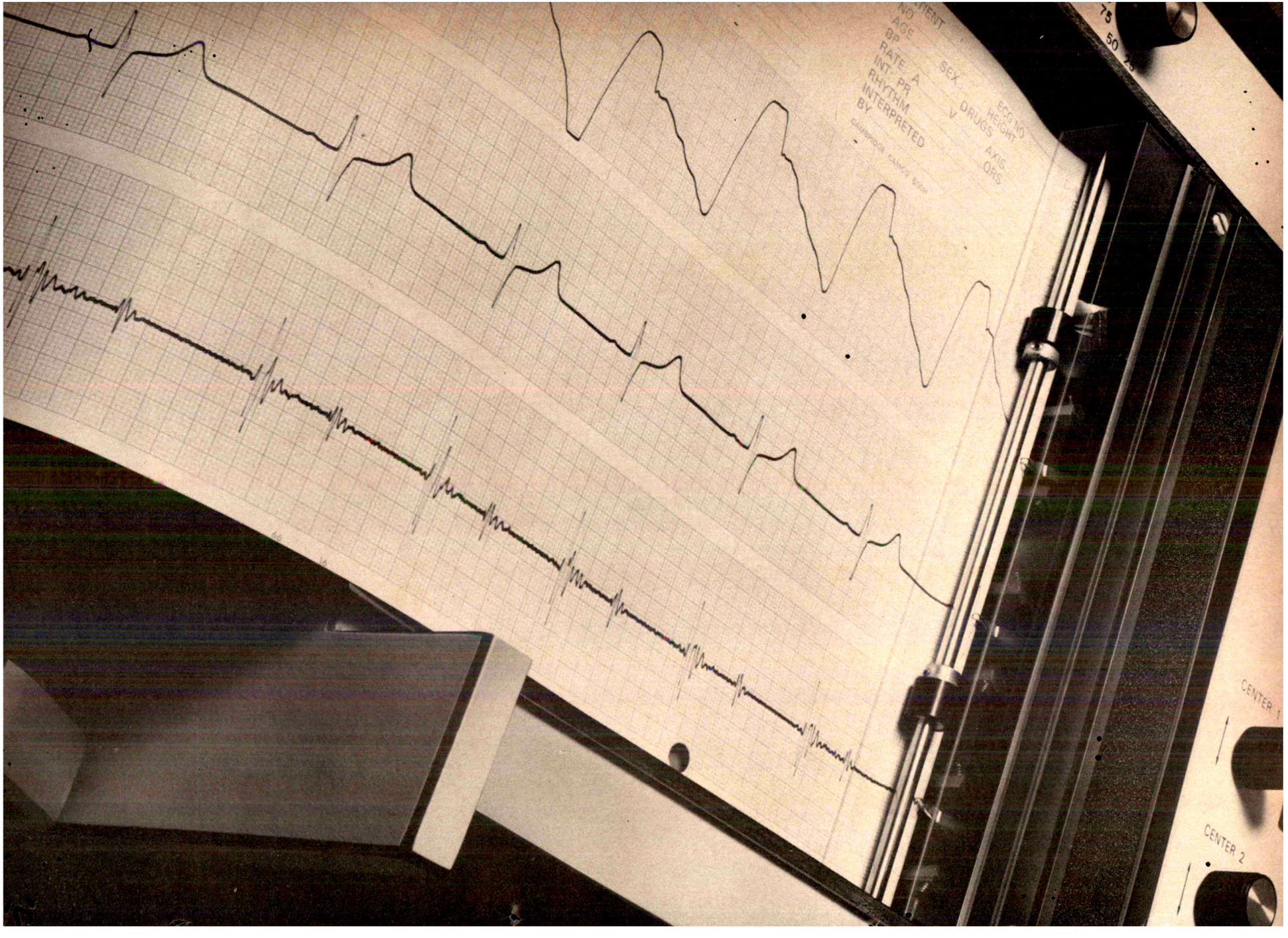
CORRECTION

A printer's error, made after release of final page proofs, resulted in inaccurate reproduction of the left panel of Figure 1 on page 2 of the July 1977 issue of the Journal (Mason JW, Myers RW, Alderman EL, et al: Technetium-99m pyrophosphate myocardial uptake in patients with stable angina pectoris. Am J Cardiol 40:1–5, 1977). The figure should have appeared as shown at right.

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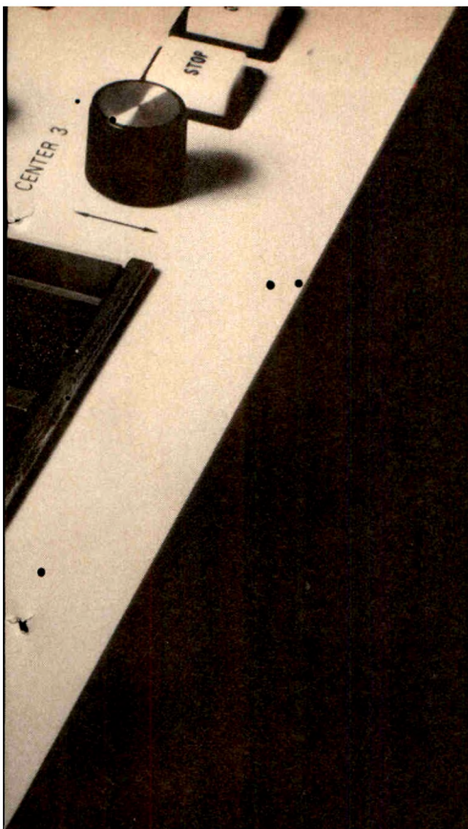

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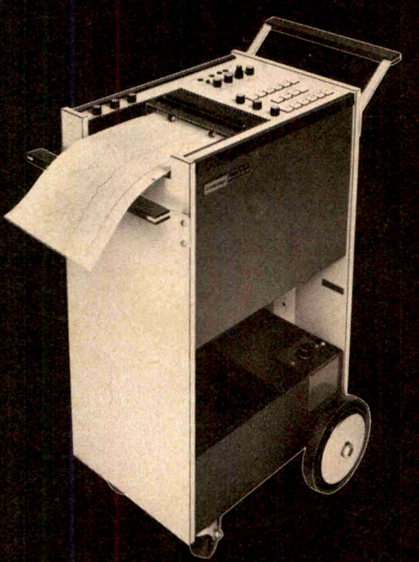

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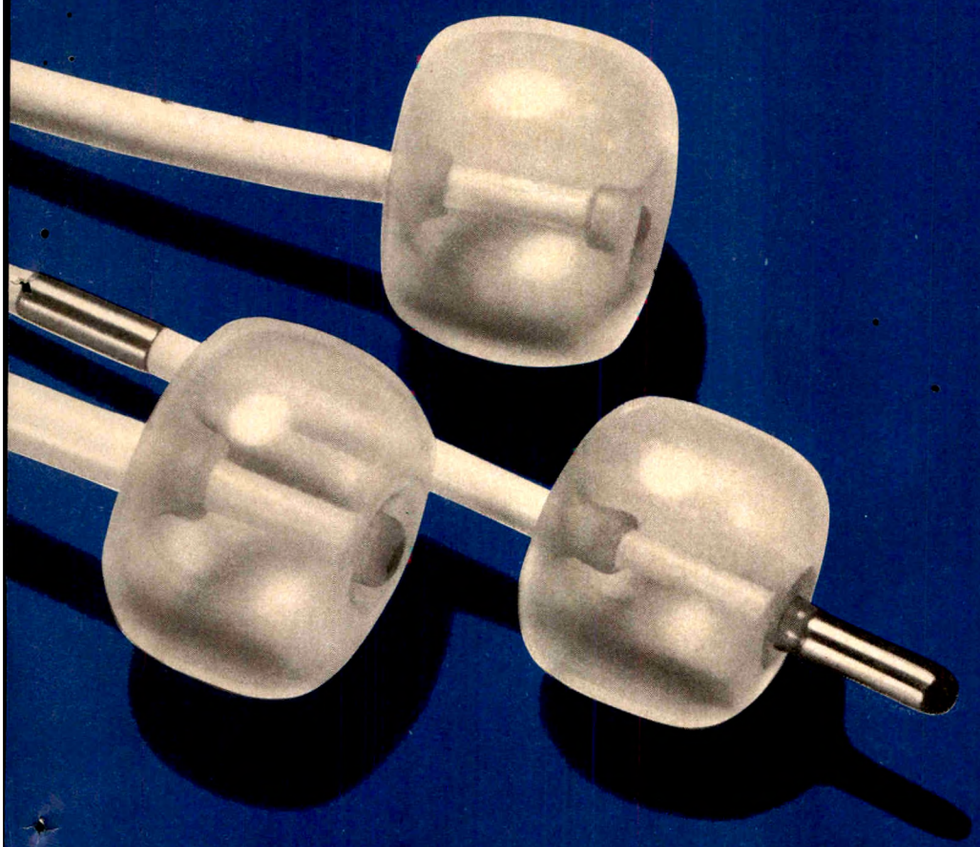

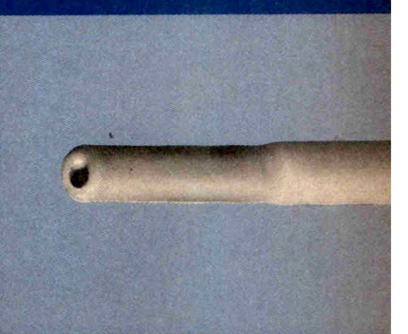

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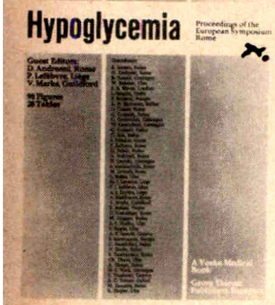

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ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

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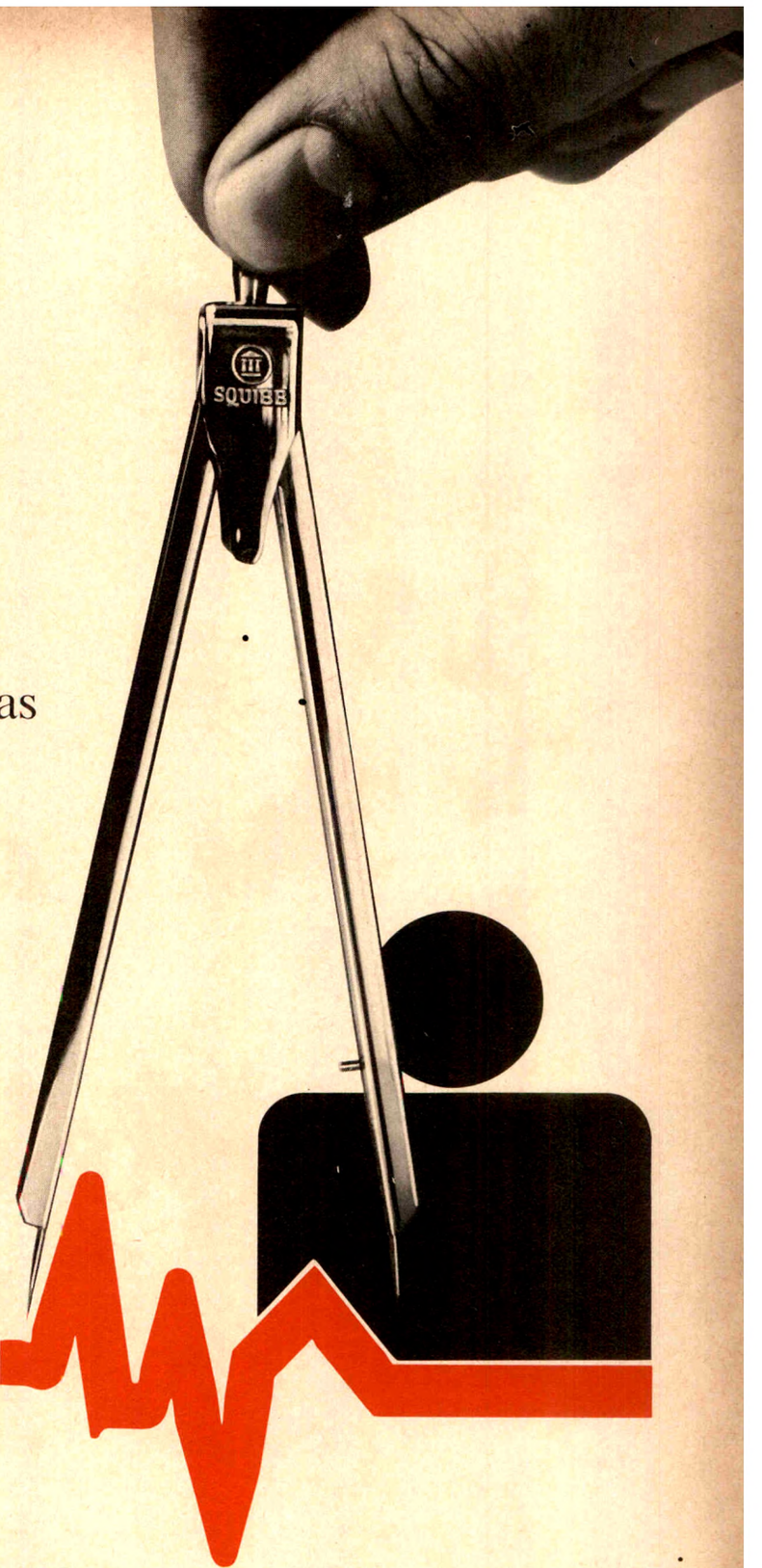

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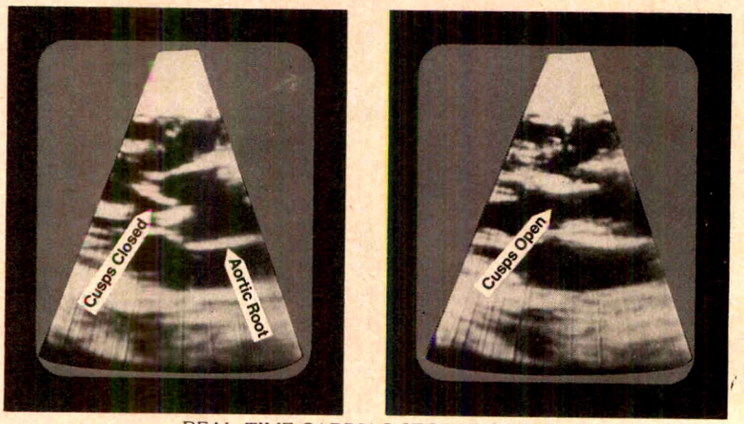

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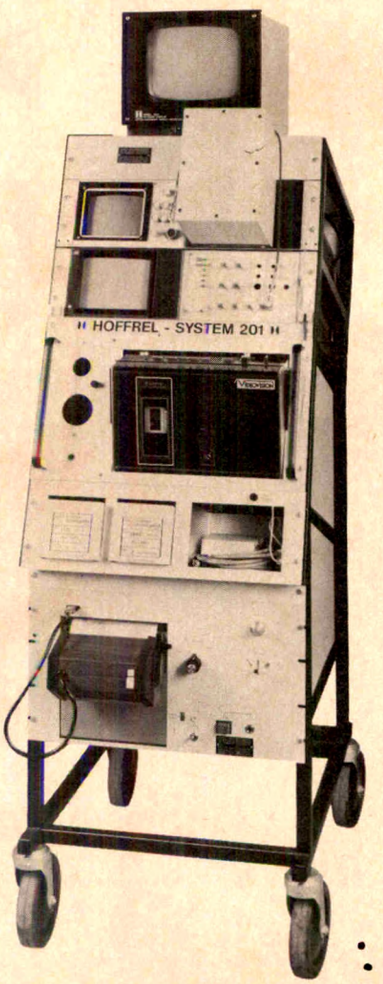

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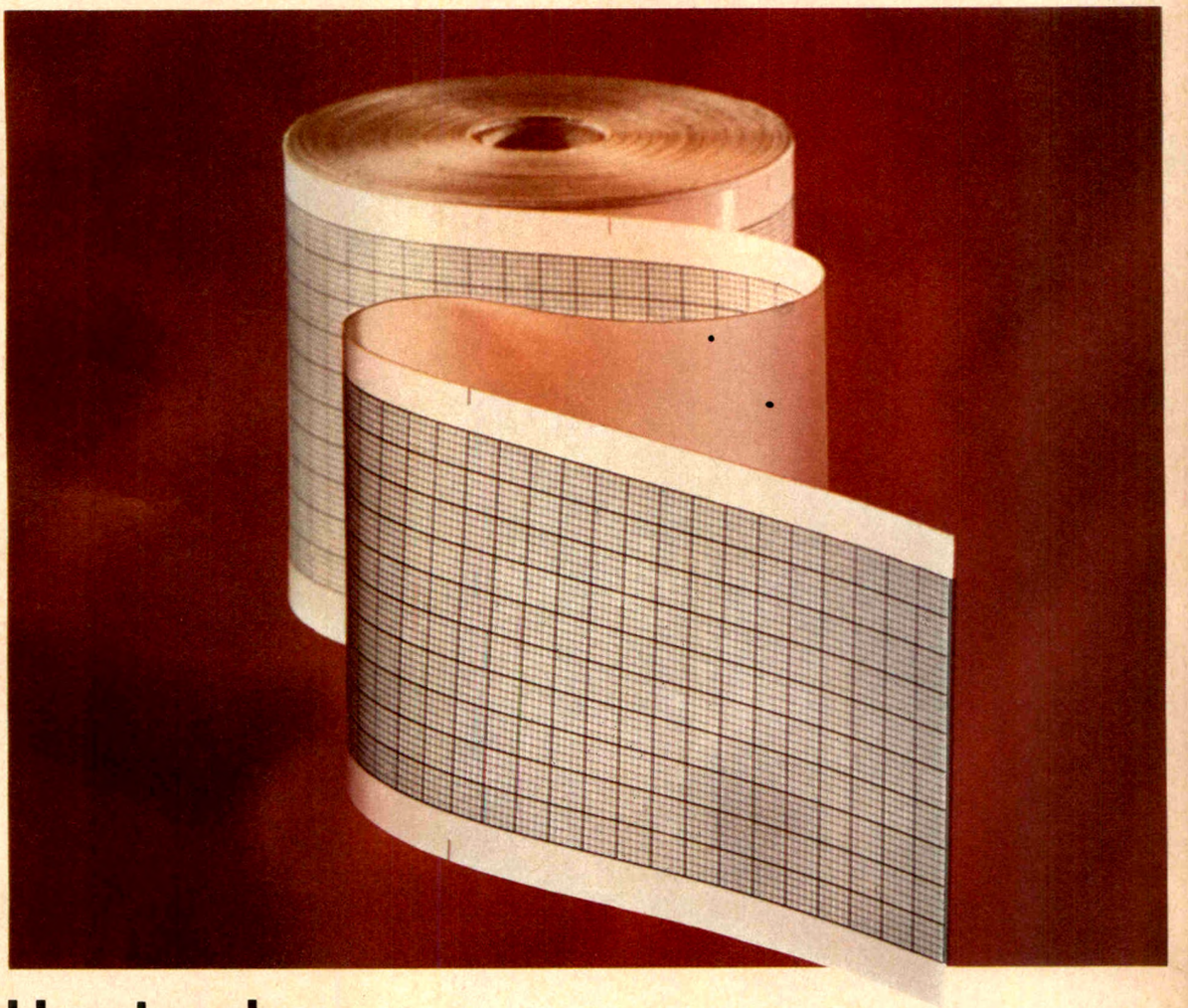

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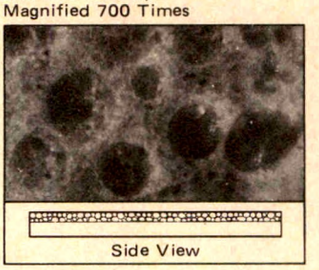

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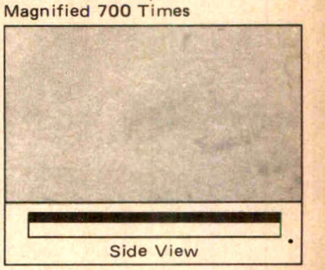

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A3

A New Vision of Catapres® (clonidine HCl)

20/20

The first 20 days

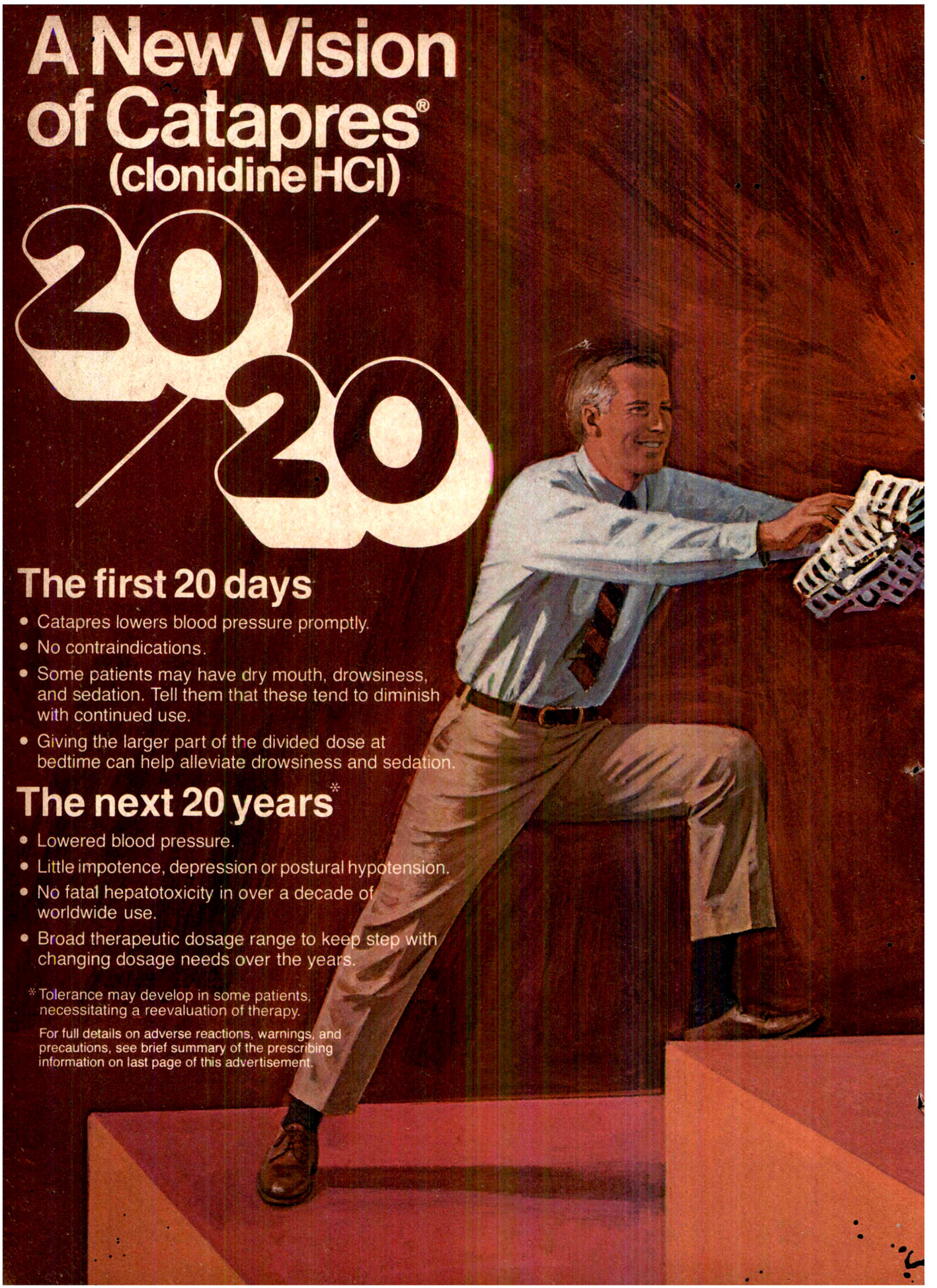
- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
- Broad therapeutic dosage range to keep step with changing dosage needs over the years.

* Tolerance may develop in some patients, necessitating a reevaluation of therapy.

For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.

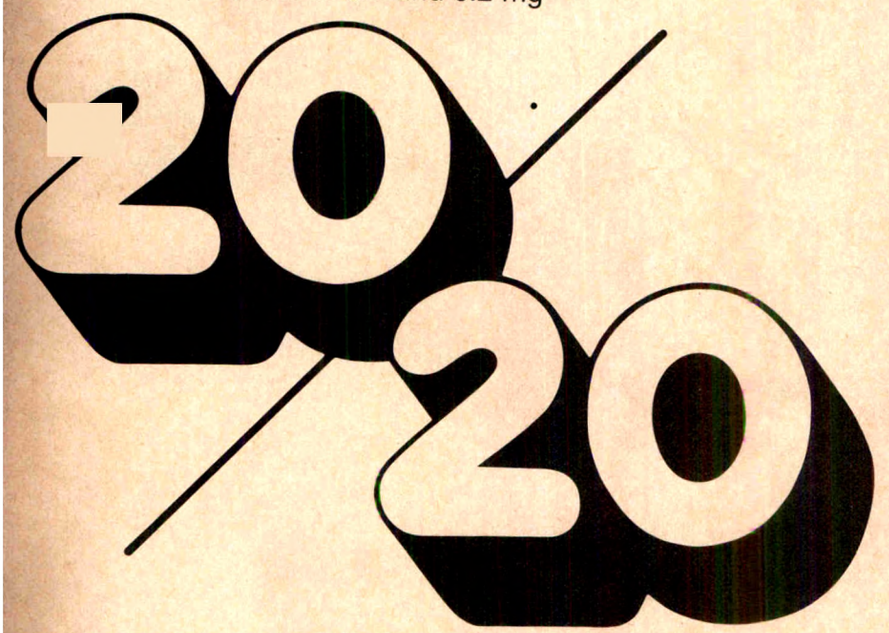


Catapres® (clonidine HCl
For Step 2 in
Hypertension

HYPERTENSION

A New Vision of Catapres® (clonidine HCl)

Tablets of 0.1 and 0.2 mg



What you do the first 20 days Can help him the next 20 years

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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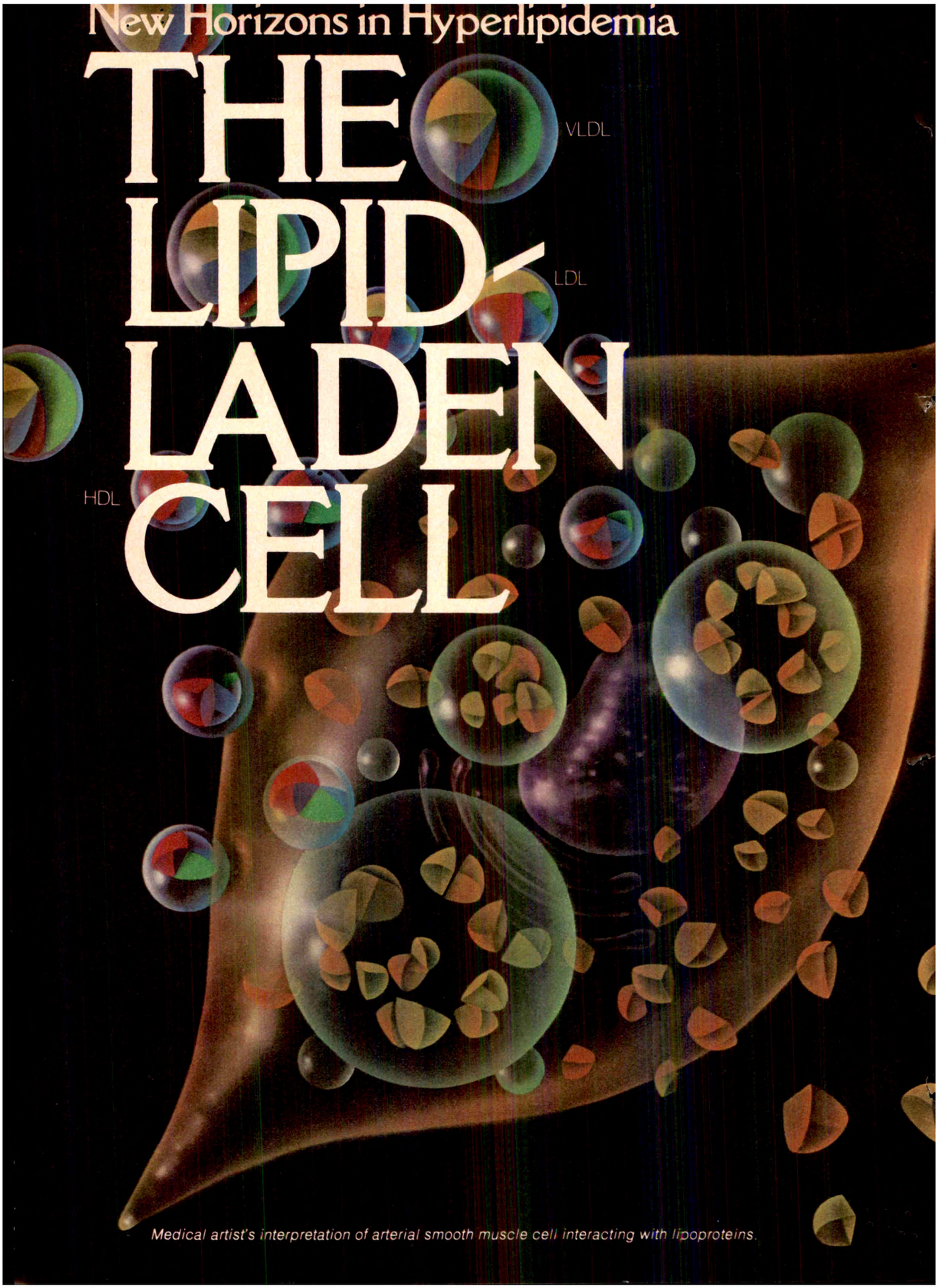
New Horizons in Hyperlipidemia

THE LIPID-LADEN CELL



Medical artist's interpretation of arterial smooth muscle cell interacting with lipoproteins.

Lipid overloading in the arterial smooth muscle cell: proposed biochemical mechanisms

The process by which a normal arterial smooth muscle cell is transformed into a lipid-laden "foam" cell is highly complex and, as yet, not completely understood. But from the findings of an ever-increasing number of animal and human studies,[1-28] investigators have begun to piece together a theoretical picture of what may occur—a picture that adds important new perspectives to an understanding of hyperlipidemia.

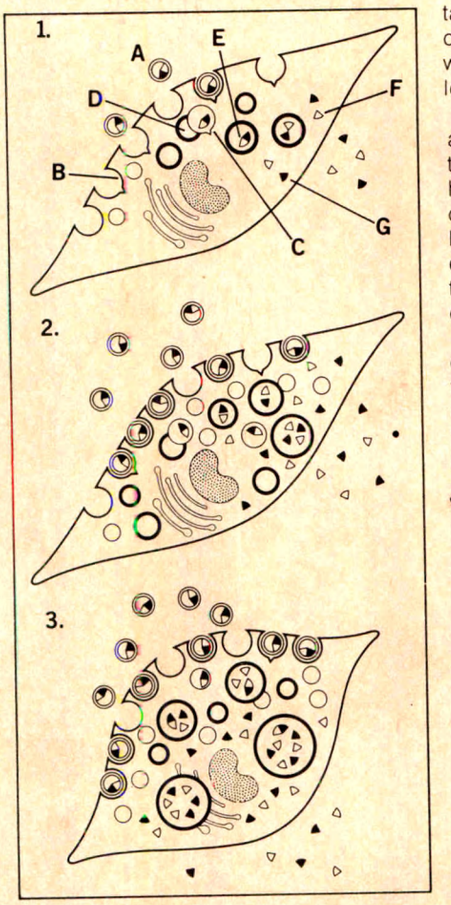
What emerges from this research is that induced and/or genetic abnormalities in the metabolism of arterial smooth muscle cells may be crucial to their evolution into a lipid-laden form.[6,9,11,19] Specifically, there appear to be alterations in the ability of these cells to bind, internalize and degrade triglyceride-rich very low density lipoproteins (VLDL) and cholesterol-rich low density lipoproteins (LDL).[1,2]

The endothelium, which normally acts as a selective barrier[20,25] to the entry of plasma constituents into the arterial wall, also appears to influence the behavior of arterial smooth muscle cells.[23,26] As a result of injury to the endothelium and/or increased concentrations of circulating lipoproteins, excessive quantities of lipids may breech the endothelial barrier, and accumulate in smooth muscle cells.[1,2,5,20,23] Eventually, the cells die and rupture, releasing their lipid content into the extracellular matrix of the arterial wall.

Human tissue cultures yield new insights into an insidious progression

Theories postulating the sequence of events that may produce lipid-laden cells were originally based on observations in a variety of animal species. Now, through the application of dramatic new biochemical techniques, many of these theories are finding support in studies of human cells. It is now possible to culture human arterial smooth muscle cells from explants of tissue obtained during vascular surgery,[1-3,10,18] human fibroblasts taken from the skin,[6,8,12,14] and human endothelial cells derived from umbilical veins.[15-17] Methods for studying the interaction of these cells with lipoproteins in culture have permitted the assessment of lipoprotein binding, uptake, and degradation.[1,2] (See diagrams at right). While this *in vitro* data requires *in vivo* confirmation, it can serve as a useful basis for investigation and discovery with regard to the relationship between plasma lipids and lipid accumulations in arterial walls.

The evolution of a lipid-laden cell: a working hypothesis[24] Disturbances in the normal metabolism of arterial smooth muscle cells can lead to marked changes in the lipid content of the arterial wall. The most notable change is an increase in cholesterol esters, but there are also increases in the concentration of other lipids, including triglycerides.[20] Following is a highly simplified outline of a working hypothesis to explain lipid overloading, as it relates primarily to LDL:[24]



1. *The arterial smooth muscle cell's natural defenses against lipid overload*[6-8,12] Given an artery with the endothelium intact, and a low level of circulating plasma lipoproteins, LDL uptake is predominantly of the high affinity, receptor-dependent type: LDL molecules (A) are bound to receptor sites (B) on the endothelial surface, internalized via pinocytotic vesicles (C), fused with lysosomes (D) which hydrolyze the cholesterol ester (E) component of the lipoprotein into its basic constituents, free cholesterol (F) and fatty acid (G). The free cholesterol triggers compensatory mechanisms which decrease cholesterol synthesis by the cell and also reduce the number of its LDL receptors, thereby helping to limit further entry of LDL. Under normal conditions, this acts to protect the arterial smooth muscle against lipid overload.

2. *The cell's response to an increased metabolic load.* Injury or disruption of the endothelium and/or a substantial increase in circulating plasma lipoproteins leads to entry of larger amounts of LDL and other lipid substances into the cells. At these higher plasma levels, lipids appear to be taken up predominantly via a low affinity, nonreceptor-mediated process.[7] Endocytosis is greatly stimulated and the number and size of the lysosomes increase in an effort to keep up with the increased load.[21]

3. *The cell's lipid-regulating mechanism overwhelmed.* If the state of increased metabolic activity needed to handle the extra lipid load persists, the "finely-tuned" regulatory mechanism may break down. With lipid passage into the cell virtually unchecked, massive intracellular accumulations of cholesterol and other lipids ensue. As a result, cellular function may be compromised, leading to cell death and deposition of lipids in the extracellular space.

High levels of circulating lipoproteins: a key factor in cellular overload

In human tissue cultures, arterial smooth muscle cells take up substantial quantities of VLDL and LDL and relatively small amounts of HDL.[1,2] This contrasts with the low uptake of VLDL and high uptake of HDL observed in smooth muscle cells of certain animal species (e.g., rats)[2] which have no propensity for lipid overloading in arterial cells.

Cellular concentrations of lipids also bear a relation to lipid concentrations in the serum. For example, both human and calf endothelial cells in tissue culture evidenced significantly higher levels of triglycerides and fatty acids after exposure to hypertriglyceridemic serum than did controls subjected to medium containing normal serum.[17]

These provocative studies have exciting implications for further investigation. *However, it must be remembered that there is to date no proof that lowering serum lipoprotein concentrations in humans will prevent or reverse the processes that produce lipid-laden cells.*

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Note: Schematic illustrations of cells adapted from Wolinsky, H.: Cardiovasc. Med. *1*:41 (Sept.) 1976.

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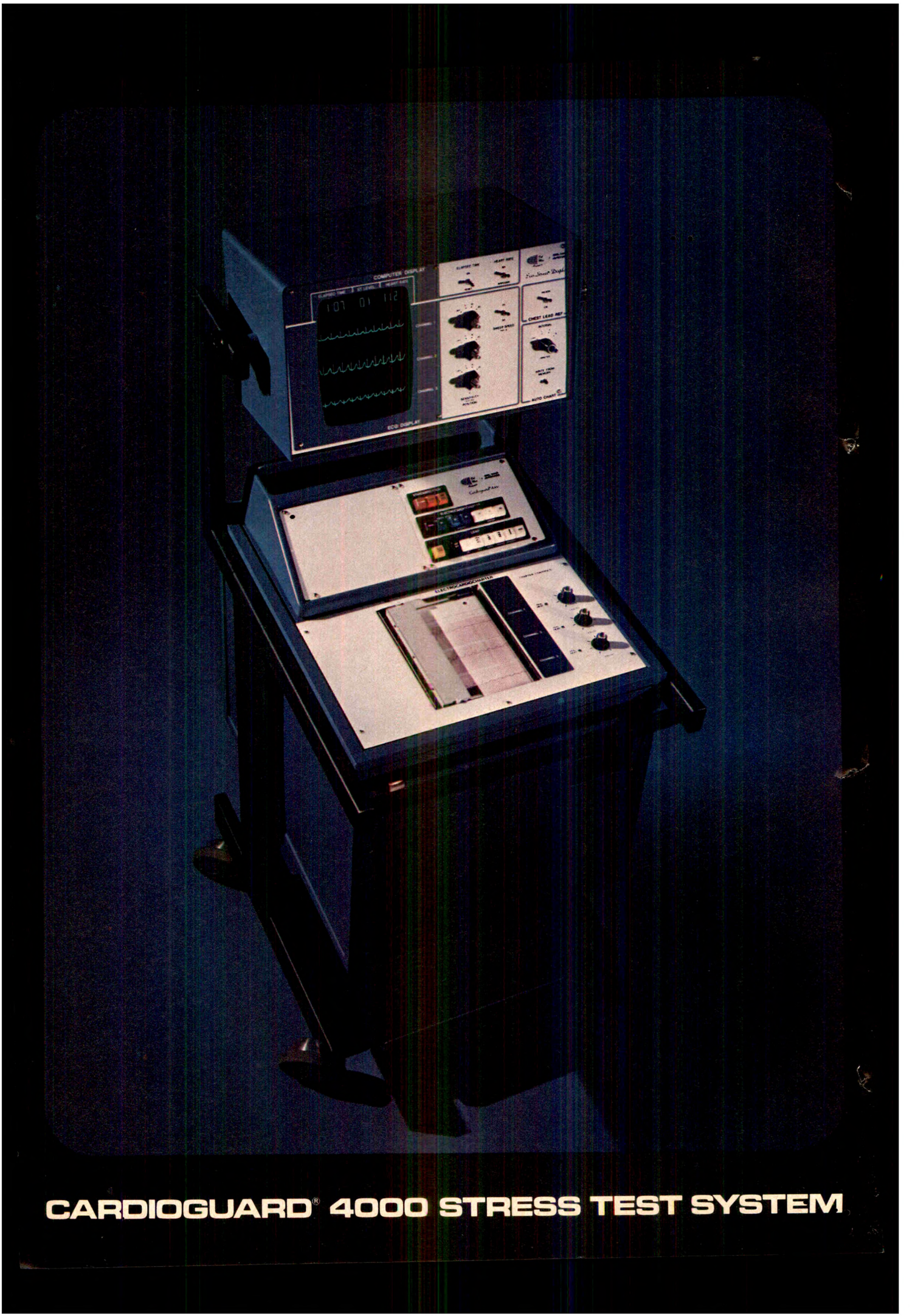

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*Not for initial therapy (see box warning). See next page for brief summary of prescribing information, including indications, contraindications and adverse reactions.

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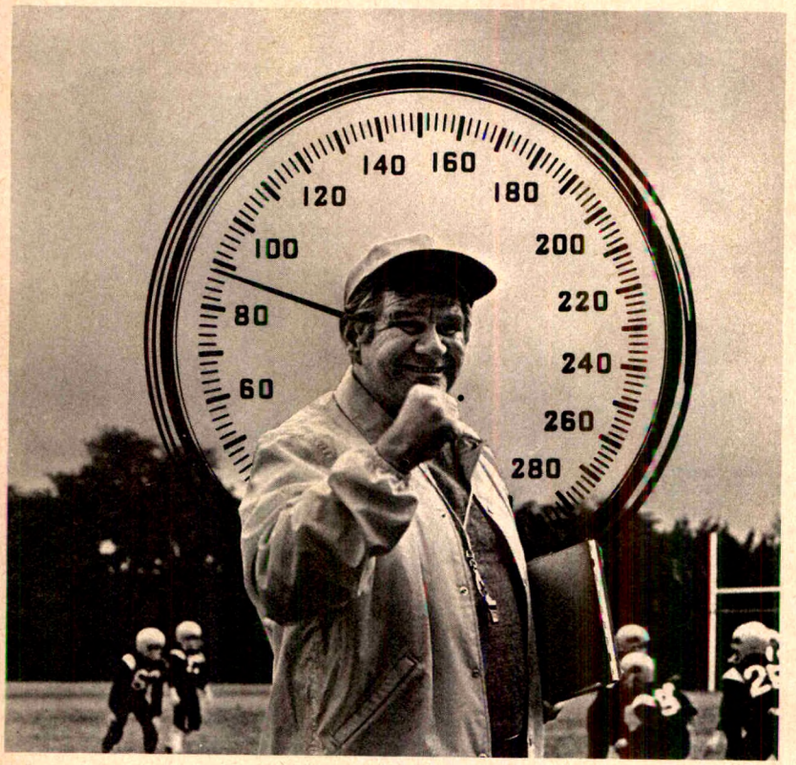

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TRIAMTERENE LIMITS POTASSIUM LOSS AS HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

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Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

*

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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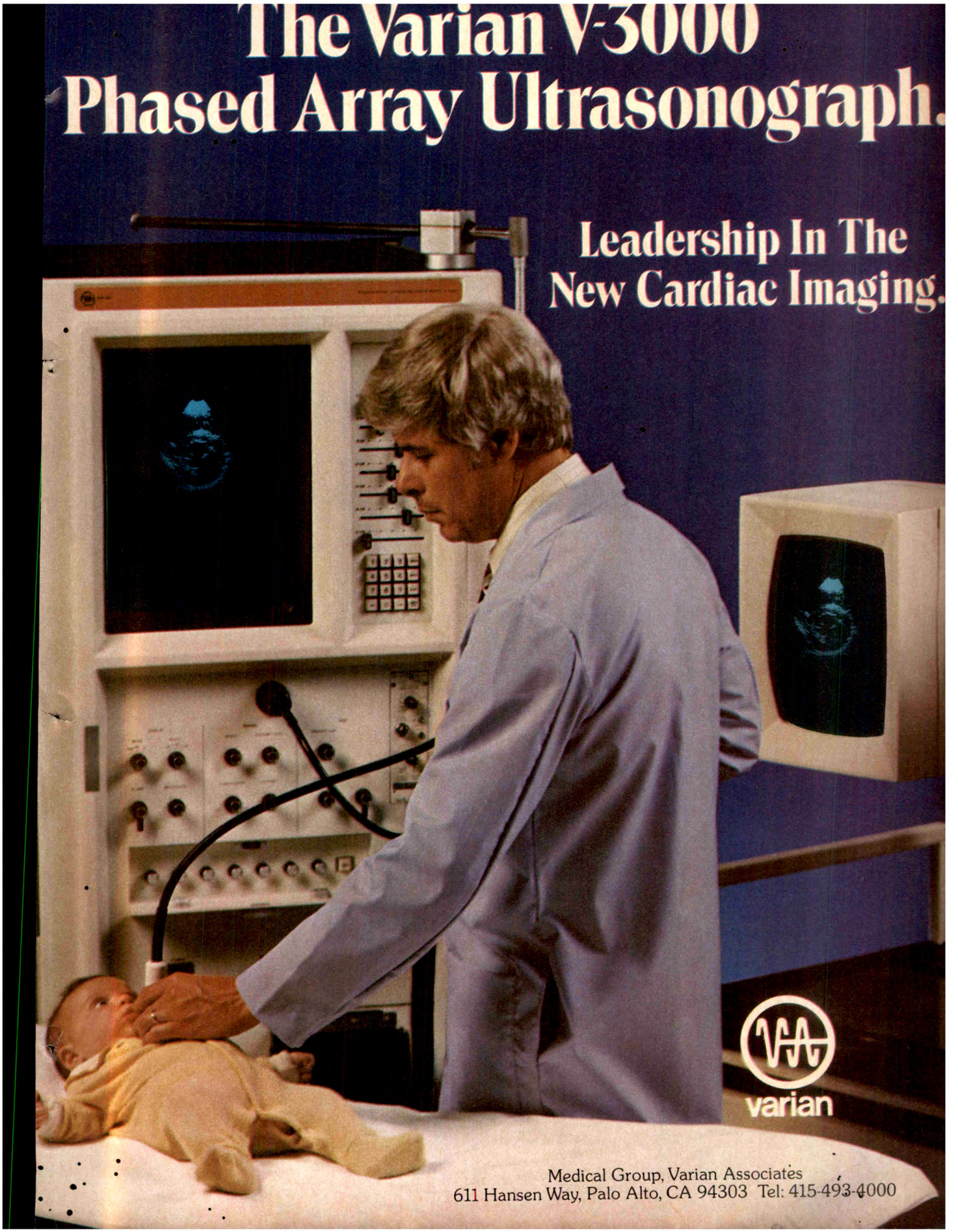

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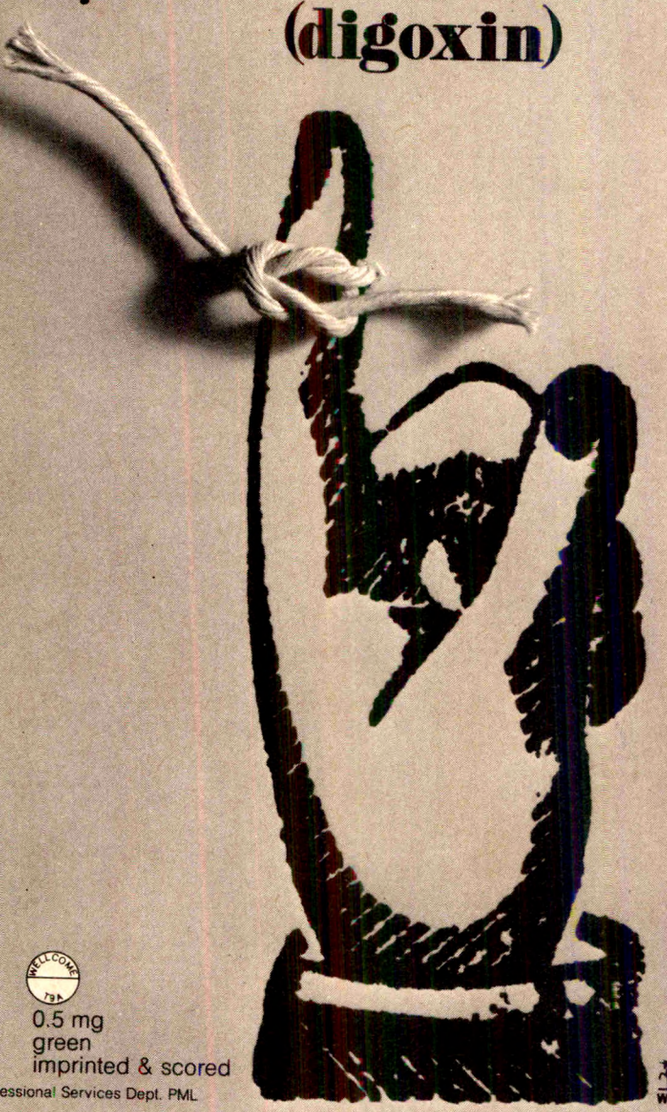

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CLINICAL STUDIES

Approach to the Estimation of Myocardial Infarct Size By Analysis of Precordial S-T Segment and R Wave Maps

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To assess the correlation of S-T segment elevations and the height of R waves of the precordial electrocardiogram with myocardial infarct size, we performed 35 lead precordial electrocardiograms (maps) in 24 patients with uncomplicated acute anterior transmural myocardial infarction. The initial analysis was carried out in 14 patients. Infarct size was estimated from the integration, from normal baseline to baseline, of serial serum creatine kinase (CK) values obtained at 2 to 4 hour intervals and expressed as IU/liter·hours. The first electrocardiographic maps were recorded 12 hours or less after the onset of symptoms. All S-T segment elevations and R waves were summed for each map (ΣS-T and ΣR). There were positive correlations between the ultimate CK infarct size and the initially recorded ΣS-T ($r = 0.69$), the initially recorded log ΣR ($r = -0.70$) and the initial early decline in log ΣR per hour [$(\Delta\log \Sigma R/\Delta hour)\cdot 10^3$, $r = 0.88$]. Therefore, these variables were combined in a multiple regression analysis: CK infarct size = $0.23\ \Sigma$S-T + $0.20\ [(\Delta\log \Sigma R/\Delta hour)\cdot 10^3] - 14.9 \log \Sigma R + 36.8$ ($r = 0.97$). In addition, on the basis of previous studies the initially recorded ΣS-T and log ΣR values were normalized with respect to time by calculating the expected ΣS-T value at 12 hours after the onset of symptoms ($\Sigma S\text{-}T_{12}$) and the 12 hour interpolated values for ΣR (ΣR_{12}). These values also showed a good correlation with infarct size: CK infarct size = $0.37\ \Sigma S\text{-}T_{12} + 0.16\ [(\Delta\log \Sigma R/\Delta hour)\cdot 10^3] - 18.2 \log \Sigma R_{12} + 40.4$ ($r = 0.97$).

To validate this approach, 10 additional patients were studied prospectively. Correlations between CK infarct size and the various measurements from the serial precordial maps were similar to those in the first study group, and CK infarct size correlated well with the electrocardiographic infarct estimates ($r = 0.90$ and $r = 0.95$, respectively). It is concluded that in selected patients CK infarct size can be directly related to the initial height of S-T segment elevations and the early rate of R wave decline and inversely related to later ΣR values, thereby providing a general approach for use in studies on the estimation of myocardial infarct size from precordial electrocardiographic maps.

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Recent studies suggest that the prognosis of patients with acute myocardial infarction is affected by the extent of myocardial damage when the latter is estimated quantitatively.[1,2] In the dog, the depletion of myocardial creatine kinase (CK) and its appearance in serum appear to have a relatively predictable relation,[3–5] and the total amount of CK released into the circulation, estimated with serial serum CK measurements, has been used in dogs and man as a measure of infarct size[1,2,4] although the reliability of this relation has been questioned in some experimental studies.[6] CK depletion has been shown to correlate relatively well with damage at the site of depletion as well as with the extent of local S-T segment change; thus, S-T segment elevations recorded from multiple epicardial leads after acute coronary occlusion were useful in predicting histologically and enzymatically determined extent of ischemic injury 24 hours after occlusion.[7,8] Studies on such correlations and the use of precordial electrocardiographic maps have been reviewed elsewhere.[9] Changes in the electrocardiographic QRS voltage have also been related to ischemic injury in dogs[10,11] and monkeys.[12] In man, however, few studies are available that attempt to correlate myocardial infarct size as estimated from serial serum enzyme levels with precordial electrocardiographic variables.[13,14]

Accordingly, we reviewed serial precordial electrocardiograms (maps) in a selected group of 24 patients with uncomplicated acute anterior myocardial infarction. The relations among S-T segment elevations, alterations in R wave voltage and infarct size estimated from serial CK values were examined retrospectively in 14 patients and validated in an additional group of 10 patients studied prospectively.

Patients and Methods

Retrospective Study

Criteria for patient selection: In the retrospective study in 14 patients, the following criteria were set for the review and acceptance of precordial electrocardiographic recordings: (1)

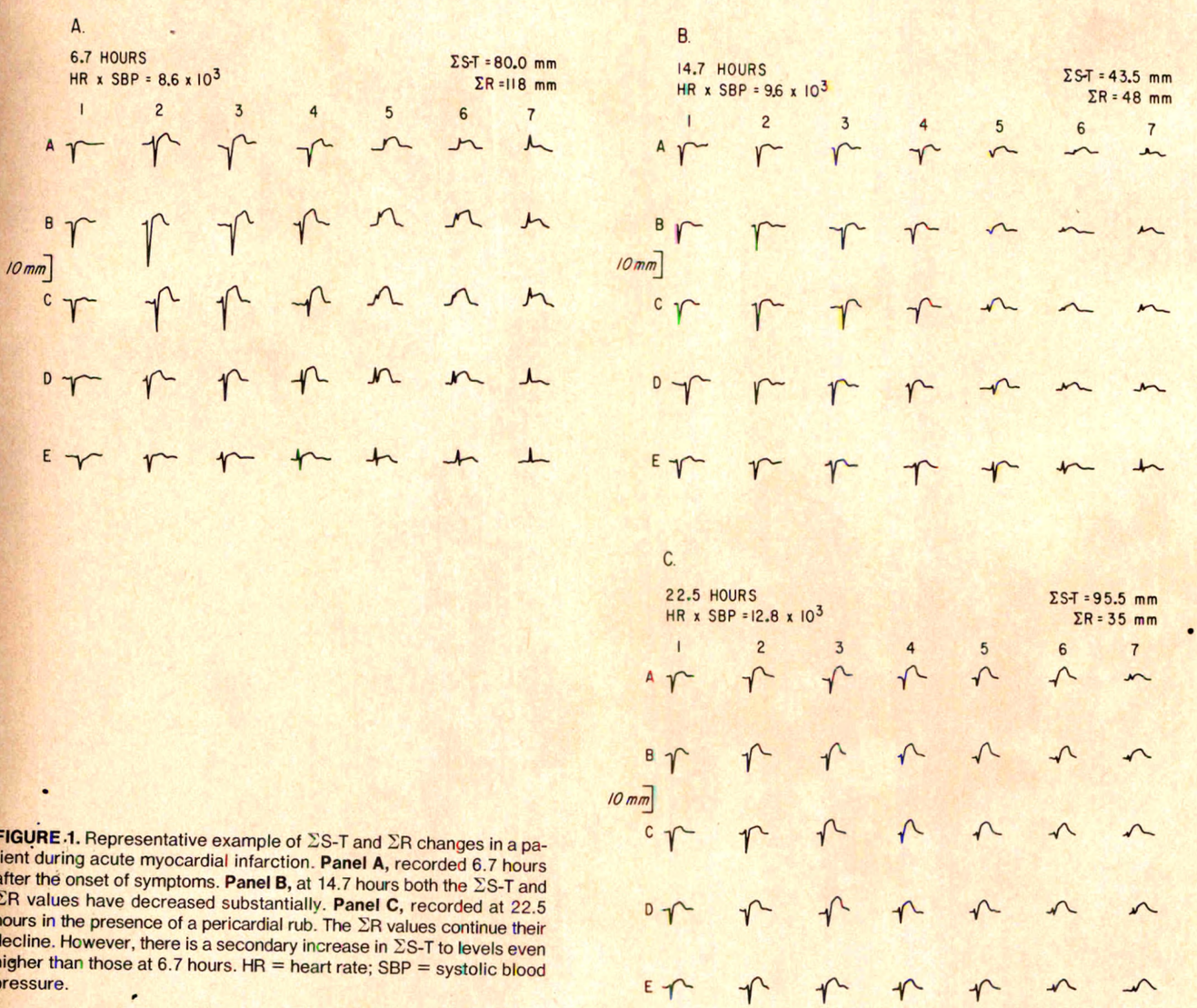

FIGURE 1. Representative example of ΣS-T and ΣR changes in a patient during acute myocardial infarction. **Panel A,** recorded 6.7 hours after the onset of symptoms. **Panel B,** at 14.7 hours both the ΣS-T and ΣR values have decreased substantially. **Panel C,** recorded at 22.5 hours in the presence of a pericardial rub. The ΣR values continue their decline. However, there is a secondary increase in ΣS-T to levels even higher than those at 6.7 hours. HR = heart rate; SBP = systolic blood pressure.

All patients included in the study had an acute transmural myocardial infarction involving the anteroseptal or anterolateral wall of the left ventricle as evidenced by a history of prolonged chest pain, characteristic elevations in serum enzymes (creatine kinase [CK], glutamic oxaloacetic transaminase [GOT] and lactic dehydrogenase [LDH]) and serial changes in 12 lead electrocardiograms. (2) No patient had a history of electrocardiographic evidence of previous infarction involving the anterior or lateral walls of the left ventricle. (3) All patients had sinus rhythm at the time of study. Precordial maps were excluded when the duration of the QRS complex exceeded 0.09 second or when a definite change in the QRS frontal plane axis occurred between two electrocardiograms. No patient had electrocardiographic evidence of left or right ventricular hypertrophy.[15] (4) In all patients the first map was recorded 12 hours or less after the onset of symptoms and at least two maps were recorded within 24 hours of the onset of symptoms. (5) All patients had an initial serum CK value within normal limits (less than 50 IU/liter) on admission. In addition, in all patients a complete CK curve obtained from serial serum CK determinations could be plotted against time from baseline to baseline. (6) No patient had clinical evidence of other systemic diseases.

Of 231 patients admitted and studied over a 3.5 year period in the Myocardial Infarction Research Unit, University of California, San Diego, 14 patients with acute anterior transmural myocardial infarction were found who fulfilled these strict criteria. (Of these, 109 patients had anterior infarction and underwent electrocardiographic mapping.) Ten were men and four women; their average age was 59.2 years. They were admitted to the coronary care unit 1 to 11 hours after the onset of symptoms (mean 4.5 hours). Four patients had a previous inferior wall infarct as judged from electrocardiographic criteria. Three patients were in clinical class I (Killip and Kimball[16] classification) on the first hospital day, 10 were in class II and 1 was in class III. No patient experienced cardiogenic shock and none had secondary increases in serum enzyme levels suggesting infarct extension. Patients with such complications were excluded from the study.

Precordial mapping and measurements: A blanket was used containing 35 unipolar electrocardiographic leads arranged in seven horizontal and five vertical rows and connected through a switch to the V lead of an electrocardiograph.[17] The upper right corner of the blanket was placed over the second right intercostal space close to the sternum and the skin was marked to assure the same location for serial studies in the same patient. The left border of the blanket was near the mid axillary line. All S-T segment elevations above baseline were measured to the nearest 0.5 mm, 20 msec after the J point, using the average of five complexes. The measured S-T elevations were summed and expressed as ΣS-T. All of the R waves in each map were likewise measured to the nearest 1.0 mm and summed and expressed as ΣR (Fig. 1).

The ΣR was plotted semilogarithmically against the time in hours after the onset of symptoms in all patients (Fig. 2). The initial hourly decline in ΣR was calculated by taking the difference between the first two log ΣR values (Δlog ΣR) and dividing by the number of hours separating the two recordings (Δlog ΣR/Δhour). For the second ΣR measurement the first consecutive map was selected that had a time difference of at least 2 hours between the two maps.

Normalization of ΣS-T and ΣR with respect to time: Because the initial precordial maps were not all recorded at the same time in relation to onset of symptoms, an attempt was made to normalize the ΣS-T and ΣR values with respect to time. Previous studies from our laboratory have shown that in patients pursuing clinically uncomplicated courses without therapeutic interventions, the mean ΣS-T values fall progressively during the first 12 hours after the onset of acute symptoms.[18] The mean ΣS-T values at 3 to 6 hours were arbitrarily set at 100 percent (actual value 72 mm), and the mean corresponding values at subsequent times are shown in Figure 3. The initially recorded S-T values were normalized with respect to time, the expected ΣS-T value at 12 hours ($\Sigma S\text{-}T_{12}$) being calculated by subtracting an appropriate percent from the initial ΣS-T value; for example, 60 percent was subtracted

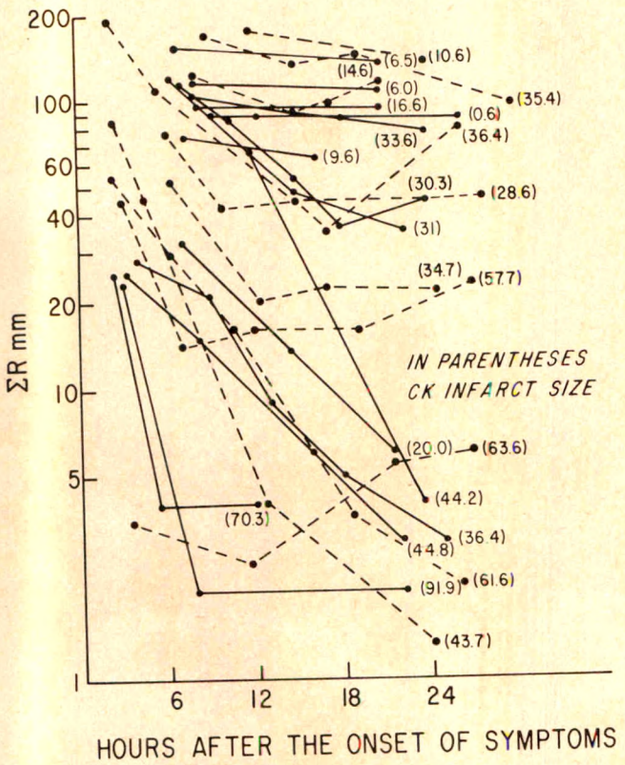

FIGURE 2. Individual changes in ΣR with time from the onset of symptoms. Numbers in parentheses indicate creatine kinase (CK)-determined infarct size. The **solid lines** represent the initial study group of 14 patients (retrospective), the **dashed lines** the validation group of 10 patients (prospective). Most ΣR values are between 70 and 200 mm.

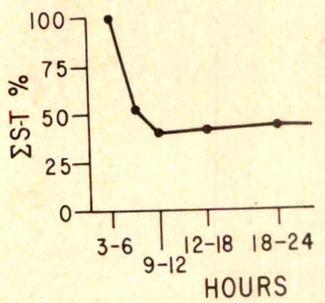

FIGURE 3. The mean percent decline in ΣS-T values 3 to 24 hours after the onset of symptoms, based on a previous study[18] of patients with uncomplicated myocardial infarction without therapeutic interventions.

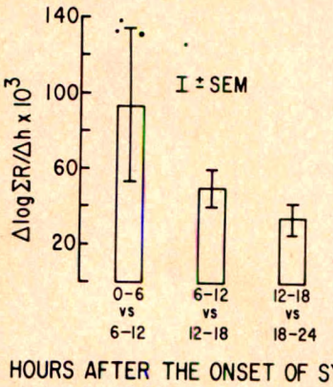

FIGURE 4. Individual ΣR slopes [(Δlog ΣR/Δhour)·10³] in relation to hours after the onset of symptoms. Each slope is obtained by comparing paired log ΣR values of adjacent time windows. The steepest declines in log ΣR values are seen between 0 to 6 and 6 to 12 hours. SEM = standard error of the mean.

for maps recorded at 3 hours, 45 percent for recordings at 6 hours, 20 percent at 8 hours, 5 percent at 10 hours and 0 percent for maps recorded at 12 hours after the onset of symptoms. The ΣR values were normalized by taking the interpolated value at 12 hours in each patient (Fig. 2). Corrected initial S-T segments rather than interpolated values were used for $\Sigma S\text{-}T_{12}$ because S-T segment elevations are susceptible to drug interventions.[7] Two patients received digoxin, 0.25 mg, during the first 24 hours after the onset of symptoms (at 8.5 and 11 hours), in four patients a trimethaphan infusion (20 to 80 mg/min) was started at 6, 9, 11 and 12 hours, respectively, and one patient received practolol (10 mg intravenously) at 11 hours, but none of these medications were administered before the recording of the first precordial map and the subsequent map used for the second ΣR measurement. A pericardial friction rub developed in three patients, but in each instance it occurred more than 12 hours after the onset of symptoms (22, 24 and 27 hours, respectively).

Creatine kinase determinations: Blood samples for CK determinations were obtained at 2 hour intervals during the first 24 hours and at 4 hour intervals after 24 hours. Blood samples (2.5 ml) were obtained in tubes containing 16λ1 millimolar ethyleneglycoltetraacetic acid (EGTA), immediately spun, and the serum was separated from the clot and quick-frozen at −70° C before storage in a −20° C freezer. Creatine kinase was assayed with Rosalki's method.[19] To obtain a measure of the extent of myocardial injury, the CK values were plotted against time in hours, the full curve between normal baseline values was integrated and the results were expressed as international units/liter × hours (IU/liter·hours). No patient received electric countershock or intramuscular injections.

Standard statistical procedures, including multiple linear regression and correlation and analysis of variance, were used to evaluate the data.

Validation: Prospective Study

To validate our approach a second group of 10 patients with acute anterior transmural myocardial infarction were studied prospectively with the same criteria used in the first study group. Seven were men and three women; their average age was 57.6 years. They were admitted an average of 4.7 hours after the onset of acute symptoms. Three patients were in clinical class I at the time of the first precordial S-T segment map, six were in class II and one was in class III. One patient had a prior inferior myocardial infarction. A pericardial friction rub occurred in two patients 24 and 42 hours, respectively, after the onset of symptoms; one patient received digoxin 19 hours after onset of symptoms, after recording of the second precordial map used for the analyses. In these prospectively studied patients, maps were recorded every 4 to 6 hours over the first 48 hours after the onset of symptoms. Complete CK curves were obtained in all.

Results

Evolution of ΣR values after the onset of symptoms: Figure 2 shows the log ΣR values plotted against time in hours in the initial 14 patients (solid lines). To obtain an estimate of the average ΣR changes over time during the first 24 hours after the onset of symptoms, this period was divided into four time windows, 0 to 6, 6 to 12, 12 to 18 and 18 to 24 hours. All individual changes in log ΣR that occurred between two adjacent time windows in the same patient were calculated to derive the individual log ΣR slopes [(Δlog ΣR/Δhour)·10³]. The mean log ΣR slopes between time windows are shown in Figure 4. The steepest declines in log ΣR occurred between 0 to 6 hours and 6 to 12 hours (mean slope 96 ± 45 mm/hour). Between 6 to 12 and 12 to 18 hours the mean slope was 49 ± 11 mm/hour and between 12 to 18 and 18 to 24 hours the mean slope was 33 ± 8 mm/hour. However, because of the wide variability in the early slopes (0 to 6 versus 6 to 12 hours), these differences in slopes did not reach statistical significance using analysis of variance for unpaired samples. Nevertheless, it is apparent from Figure 2 that in two patients with the largest infarct sizes, the ΣR values had diminished maximally by 9 hours, and no further changes were seen after the very steep early decline. Conversely, the patients with a CK infarct size of less than 10 IU/liter·hour showed small ΣR changes, although a slight decline in ΣR values was observed in all cases. Most of the other patients showed an uninterrupted decline in log ΣR values during the first 24 hours.

The decline in log ΣR was similar in the validation group of 10 patients (Fig. 2, dashed lines). These patients were studied at shorter time intervals (at least every 6 hours for 48 hours after the onset of symptoms). In 9 of 13 patients from both study groups who had precordial maps recorded beyond 24 hours, increases in ΣR after the early decline were observed. This increase in ΣR occurred between 12 and 32 hours (mean 22 hours) after the onset of symptoms.

Correlations of ΣS-T and ΣR values with CK infarct size: Table IA shows the initially recorded ΣS-T values, the first and second recorded ΣR values, the initial log ΣR slope, the normalized ΣS-T values, the log ΣR value taken at the individual intercepts with the 12 hour time line (ΣR_{12}) and the CK infarct size for the initial 14 patients.

A correlation was found between the first recorded ΣS-T value and infarct size ($r = 0.69$), and a fair correlation ($r = 0.47$) existed between $\Sigma S\text{-}T_{12}$ and CK infarct size. The initially recorded log ΣR showed a negative correlation with infarct size ($r = -0.70$) and using the

TABLE I

Summary of Data

Case no.	Initial Map (hours after onset of symptoms)	Initial ΣS-T (mm)	Initial ΣR (mm)	Second Map (hours after onset of symptoms)	Second ΣR (mm)	$\frac{\Delta \log \Sigma R}{\Delta \text{ hour}} \cdot 10^3$	ΣS-T_{12} (mm)	log ΣR_{12}	CK Infarct Size (IU/liter·hour)
A. Initial Group: 14 Patients									
1	10.5	8.0	88	18.7	85	1.1	8	1.94	0.6
2	8.2	9.0	110	21.0	104	1.6	7	2.03	6.0
3	7.0	10.5	153	21.0	132	4.3	7	2.16	6.5
4	7.5	18.0	72	16.5	62	6.7	12	1.83	9.6
5	8.5	58.5	96	21.0	92	1.6	47	1.97	16.6
6	7.2	18.0	32	14.5	13	53.4	12	1.26	20.0
7	7.0	21.0	112	10.5	85	34.3	14	1.86	30.3
8	6.7	80.0	118	14.7	48	47.0	54	1.81	31.0
9	8.0	79.0	102	16.0	89	7.5	63	1.95	33.6
10	4.0	24.0	28	9.0	21	24.0	10	1.04	36.4
11	12.0	45.0	65	23.5	4	105.2	45	1.81	44.2
12	3.5	77.0	25	8.0	15	48.9	31	0.95	44.8
13	2.3	15.5	25	5.5	4	250.0	6	0.60	70.3
14	3.0	164.0	23	8.0	2	212.0	66	0.30	91.9
B. Validation Group: 10 Patients									
1	12.0	17.5	158	18.5	13	11.7	17.0	2.19	10.6
2	8.0	30.1	122	12.0	100	22.5	19	2.00	14.6
3	6.0	7.2	79	10.0	43	67.5	4	1.63	28.6
4	6.5	3.0	51	12.5	20	67.5	2	1.35	34.7
5	9.5	73.6	180	15.5	130	14.0	53	2.24	35.4
6	2.0	171.7	194	5.0	174	16.5	81	1.75	36.4
7	2.5	75.1	85	4.5	46	135.0	26	1.59	43.7
8	3.0	146.0	46	7.0	15	25.0	78	1.23	57.7
9	2.5	89.2	65	6.5	30	85.0	39	1.16	61.1
10	3.5	78.0	4	9.2	2	42.0	44	0.40	63.6

Measurements from precordial electrocardiograms and serum creatine kinase (CK) curve analysis. Initially recorded ΣS-T values, serially recorded ΣR values, initial log ΣR slope, ΣS-T and log ΣR values at 12 hours are shown for the initial 14 patients (**A**, 14 patients) and for the validation group (**B**, 10 patients).

12 hour interpolated values (log ΣR_{12}) improved the correlation substantially ($r = -0.84$). The initial log ΣR slope [(Δlog ΣR/Δhour)·10^3] also showed a good correlation with the eventual infarct size ($r = 0.88$). Thus, patients with a large myocardial infarct tended to show high initial ΣS-T values and steep descents of log ΣR during the first 12 hours after the onset of symptoms, as well as low log ΣR values at 12 hours.

The initially recorded variables were combined in a multiple regression analysis which showed an improved correlation ($r = 0.97$) with CK infarct size in comparison with the single variables:

$$\text{CK infarct size} = 0.23\ \Sigma\text{S-T} + 0.20[(\Delta\log \Sigma R/\Delta\text{hour}) \cdot 10^3] - 14.9 \log \Sigma R + 36.8 \quad (1)$$

Multiple regression analysis was also performed using the time-normalized values ΣS-T_{12} and ΣR_{12} and yielding an r value of 0.97:

$$\text{CK infarct size} = 0.37\ \Sigma\text{S-T}_{12} + 0.16[(\Delta\log \Sigma R/\Delta\text{hour}) \cdot 10^3] - 18.2 \log \Sigma R_{12} + 40.4 \quad (2)$$

Figure 5A illustrates the relation of infarct size to initially recorded ΣS-T and ΣR values using Equation 1, and Figure 5B shows the relation between the electrocardiographic variables and CK infarct size, using the time-corrected values (Equation 2). The mean absolute difference between the calculated infarct size using the electrocardiographic data in Equation 1 and the observed infarct size by CK criteria was 4.9 IU/liter·hour, or 15 percent of the mean infarct size (31.6 ± 6.9 IU/liter·hour). The mean absolute difference calculated using Equation 2 was identical.

Validation: Table IB shows the ΣS-T and ΣR values and the initial log ΣR slope and the CK infarct size for the 10 patients studied prospectively. Correlations between the CK estimate of infarct size and the ΣS-T and ΣR measurements were similar to those in the initial study group. CK infarct size correlated well with the first recorded ΣS-T ($r = 0.69$) but was only fair with ΣS-T_{12} ($r = 0.50$). The initially recorded log ΣR showed a negative correlation with CK infarct size ($r = -0.65$), and this improved with the 12 hour interpolated values (log ΣR_{12}, $r = -0.82$); the correlation was not good when the initial log ΣR slope was used ($r = 0.35$).

Figure 5A shows the relation of CK infarct size to the initially recorded ΣS-T and ΣR values (Equation 1) for the 10 patients ($r = 0.90$). There was also a good correlation between CK infarct size and the time-corrected electrocardiographic variables (Equation 2, $r = 0.95$) (Fig. 5B). The mean absolute difference between the calculated infarct size from the electrocardiographic variables (Equation 1) and the CK infarct estimate was 3.5 IU/liter·hour, or 9 percent of the mean CK infarct size (38.6 ± 18.0 IU/liter·hour); the mean absolute dif-

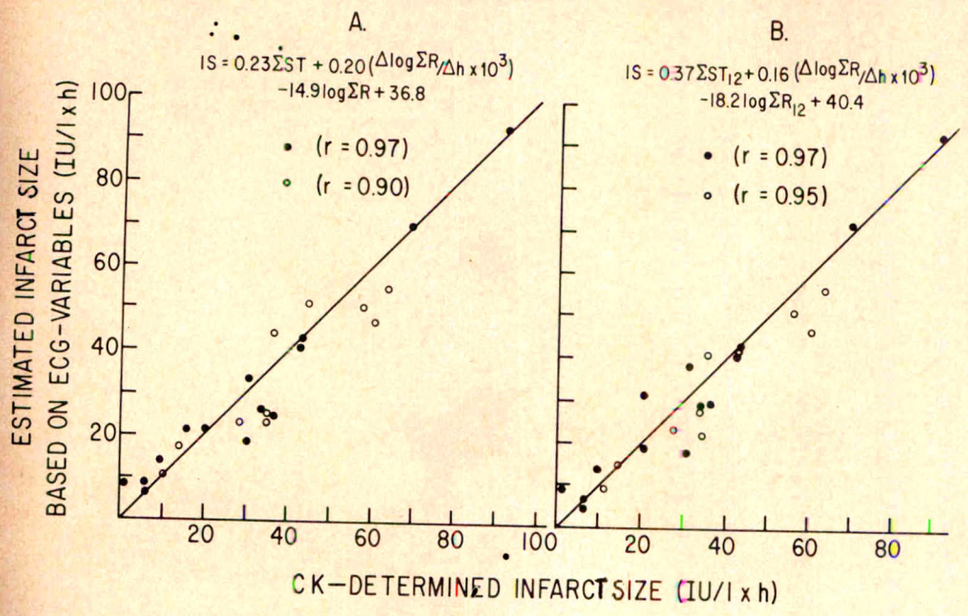

FIGURE 5. The correlation between electrocardiographic (ECG) variables [ΣS-T, log ΣR and (Δlog ΣR/Δhour)·10³] and creatine kinase (CK) infarct size, using the initially recorded data (**A**) and time-corrected values (**B**). The **solid dots** represent the initial study group (14 patients) and the **open circles** the validation group (10 patients). **Diagonal lines** represent the lines of identity. Similar correlations were found for the study group and the validation group. IU/l × h = international units/liter·hour.

ference using Equation 2 was 5.2 IU/liter·hour (13 percent of the mean CK infarct size).

The correlation between the eventual infarct size by CK curve analysis and the initially recorded log ΣR was fair for the total group of 24 patients ($r = -0.63$), improved when correlated with log ΣR at 24 hours ($r = -0.74$) and was best at 48 hours ($r = -0.82$). Thus, in the total group ΣR values recorded 24 hours or more after onset of symptoms correlated better with CK infarct size than earlier ΣR measurements (initial log ΣR, ΣR at 12 hours).

Discussion

Accurate and early prediction of the eventual size of an acute myocardial infarction would, or course, be of considerable value in evaluating and guiding therapy in patients with this condition. Several methods have been utilized to estimate completed infarct size in man[1,2,17,20–23] and in experimental animals[3,7,22,24] and have included S-T segment mapping,[1,7,17] radionuclide imaging[20,21,24,25] and analysis of serum creatine kinase (CK) values.[1–3,22,23] Prediction of the eventual infarct size from early serum CK values[4] or by curve fitting has not yet received general acceptance[26]; however, the method used in our study for estimating infarct size from CK data does not involve estimation or prediction of the fractional decay rate of CK. Bleifeld et al.[23] have recently reported a close correlation between total CK release and morphologic ischemic damage in patients at postmortem examination.

The correlation found in this study between infarct size estimated from completed CK curves and ΣS-T suggests that a relation similar to that observed experimentally[7,9,11,27] may exist in man using precordial S-T segment mapping. This finding contrasts with a recent report by Norris et al.[13] A recent analysis by Holland and Brooks[28] using a single centrally placed electrode indicates that precordial and epicardial S-T segment deflections are complex functions of the geometric size and shape of the ischemic zone, the extent of the latter being directly related to precordial S-T segment elevations but inversely related to epicardial S-T elevations. Their study is difficult to compare with investigations in closed chest dogs in which S-T segment changes in multiple epicardial and precordial leads were compared and found to correlate closely during several acute interventions.[29] The problem might be elucidated by solid angle analysis in the dog using multiple electrocardiographic leads. Furthermore, the influence of conduction disturbances needs further study.[9]

R wave amplitude and size of myocardial infarct: A decrease in the amplitude of epicardial R waves within 4 hours of coronary occlusion was first reported by Johnston et al.[30] Subsequently, Prinzmetal and coworkers[31,32] showed that epicardial sites associated with a decrease in R wave amplitude were characterized by a variable mixture of viable and necrotic myocardial tissue, and Myers et al.[33,34] in clinical studies demonstrated that the larger the infarct the more widespread were the presence of Q waves and the disappearance of R waves. Muller et al.[29] found a decrease of 31 percent in epicardial R wave height in ischemic areas 15 to 60 minutes after coronary occlusion in dogs. Additional studies in monkeys[12] and dogs[10] showed a progressive loss of QRS voltage and bipolar potential electromotive force after coronary occlusion with stabilization at 6 hours. The results of our study suggest that the R wave amplitude declines most rapidly in patients with large infarcts, and that at 12 hours after the onset of symptoms their ΣR values may be smaller than those of patients with small infarcts. The timing of the steep early decline in log ΣR values in two patients of the initial study group with the largest infarcts was similar to that of the R wave changes that Smith et al.[12] described in monkeys after coronary occlusion. In addition, Cox et al.[10] recorded intramyocardial bipolar potentials in dogs

after coronary occlusion and found that sites with the greatest loss of electromotive force also demonstrated the greatest degree of histologic injury. Both studies showed that reperfusion up to 6 hours after coronary occlusion resulted in a partial preservation of QRS voltage. Recently, Hillis et al.[11] reported on the interrelation of S-T segment elevation and subsequent changes in R and Q waves after coronary arterial occlusion. In their study early S-T elevation predicted changes in R and Q waves 24 hours after coronary occlusion, and the decrease in R wave height and the development of Q waves correlated with the histologic extent of necrosis and myocardial CK depletion. This finding is similar to our observation that the decline in ΣR and ΣR at 24 hours and later after the onset of acute symptoms correlate with myocardial CK release as assessed from completed serum CK curves.

Correlation of CK infarct size and ΣR and ΣS-T: The wide range of CK infarct size and the variable initial study time did not allow a good correlation between CK infarct size and the initial ΣR value, but good correlations with ΣR were obtained in our study when ΣR was measured at 24 and 48 hours. This may be related to the fact that late increases in ΣR after the initial decline were observed in some patients. These patients received no drug therapy, and no complications or conduction abnormalities occurred; the reason for such recovery of ΣR is not clear. Prinzmetal et al.[31] and Shaw et al.[32] found an early increase in the height of R waves after coronary occlusion in some experiments, which may be explained by localized conduction abnormalities.[29] Such early increases in R waves were not observed in our patients, but no maps were recorded during the first 2 hours after the onset of infarction.

Our study demonstrated a correlation between infarct size estimated from serial CK measurements and three electrocardiographic variables: ΣS-T, log ΣR and rate of decline of log ΣR. Furthermore, multiple regression analysis showed that a combination of these variables yielded a correlation with infarct size that was superior to that of any single variable, and this approach was validated in a prospective study of 10 patients. A similar approach might be of value for the prediction of infarct size early in a patient's course, permitting the evaluation of therapeutic interventions designed to limit myocardial infarct size. For this purpose, two precordial recordings at least 3 hours apart would be required to obtain control values of ΣS-T, log ΣR and Δlog ΣR/Δhour.

In our study, the mean absolute difference between the electrocardiographically estimated severity of ischemia and the CK infarct size was 4.9 ± 1.0 IU/liter·hour, using both Equations 1 and 2; a similar difference was found in the second, prospectively studied group. This finding suggests that a group of 10 to 15 patients with a control group of equal size would suffice to reveal a statistically significant mean reduction of infarct size of 5 IU/liter·hour at the 5 percent probability level in the patient group receiving a therapeutic intervention. Although time correction (Equation 2) did not result in an improved correlation with CK infarct size compared with that obtained with Equation 1, it is possible that better results could be obtained if actual rather than interpolated values were used.

Clinical implications: It is uncertain how applicable the present approach might be in a more heterogeneous group of patients comprising persons with left ventricular hypertrophy or previous myocardial infarction involving the anterior, lateral or posterior walls of the left ventricle, or acute anterior infarction extending inferiorly or posteriorly. Probably, however, Equations 1 and 2 would have to be modified to include such patients. The use of vectorcardiographic approaches should also be explored. The log ΣR slopes are unknown for patients studied very early (0 to 2 hours), as well as for patients with small infarcts (who tended to have milder symptoms and to be admitted later than patients with large infarcts). Also, it is apparent from Figure 2 that the decline in ΣR values was not completed in most patients at the time of the first map, which was obtained not later than 12 hours after the onset of symptoms. However, no further decline in ΣR was observed in two patients with a large CK infarct size sooner than 12 hours after the onset of symptoms. It is possible that in future studies a time limit for the initial ΣR in reference to the onset of symptoms and a lower limit for the absolute value of the initial ΣR should be defined in a larger group of patients before applying such electrocardiographic analysis in predictive studies.

Despite these limitations, this small retrospective study in 14 patients and the prospective study of 10 patients indicate that the ΣS-T value and the rate of R wave decline in the precordial electrocardiogram can be reliably related to infarct size estimated from complete CK curves. The potential significance of these correlations for early prediction of infarct size and for assessment of the effects of therapeutic interventions will require further evaluation in a larger number of patients in a more diverse population.

Acknowledgment

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Computerized Orthogonal Electrocardiogram: Relation of QRS Forces to Left Ventricular Ejection Fraction

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Several studies have suggested a relation between Q wave or R wave amplitude in the standard 12 lead electrocardiogram and the left ventricular ejection fraction. Accordingly, we analyzed the relation between Q wave and R wave amplitudes obtained with computerized orthogonal (Frank) electrocardiography and the angiographically determined left ventricular ejection fraction. A computerized orthogonal electrocardiogram was obtained before cardiac catheterization in 52 consecutive patients being evaluated for chest pain. The electrocardiographic diagnosis indicated 14 normal tracings, 20 inferior, 12 anterior and 6 lateral myocardial infarctions. Linear correlations were made between X, Y and Z axis lead voltages and ejection fraction. A significant correlation was obtained between the voltages of the R waves in the X, Y and Z leads (Rx, Ry, Rz) and of the Q waves in lead Z (Qz) as well as total amplitude Qx + Rx, Qy + Ry and ejection fraction ($P < 0.01$). Arithmetic summation of Rx + Ry + Qz (ΣR) significantly augmented the correlation with ejection fraction ($r = 0.78$, $P < 0.001$); this was only slightly improved by multivariate analysis of Rx, Ry, Qz ($r = 0.80$, $P < 0.001$) or Rx, Ry, Rz, Qx, Qy, Qz ($r = 0.82$, $P < 0.001$). ΣR, utilized as a means of predicting whether an ejection fraction was more or less than 50 percent, had an accuracy rate of 92 percent. Thus, ΣR contains important information that can be used practically in the precatheterization evaluation of patients with chest pain and follow-up evaluation of patients with myocardial infarction.

In recent years a large volume of clinical and experimental information has shown an interrelation among electrocardiographic, biochemical and functional changes that occur in the acutely ischemic myocardium.[1–5] Earlier observations were concerned with S-T segment variations as measures of the extent of acute injury; more recent attention has been focused on QRS changes.[2,3] Several studies[4,5] have suggested that QRS forces in the standard 12 lead electrocardiogram or precordial maps also relate to ventricular function in chronic ischemic heart disease. These observations led us to explore the computerized orthogonal electrocardiogram as an index of left ventricular function. Because the orthogonal electrocardiogram gives equal representation to potentials in the frontal, sagittal and horizontal planes it is not limited to anterior forces as in recordings from precordial blankets nor is it encumbered by the problem of weighing six precordial against the remaining leads of a standard 12 lead electrocardiogram. Computer readout also eliminates observer bias and variation in assessing the presence and magnitude of normal and abnormal QRS forces.

We report herein the relation between orthogonal resting electrocardiographic forces and the left ventricular ejection fraction in a series of patients who underwent diagnostic cardiac catheterization.

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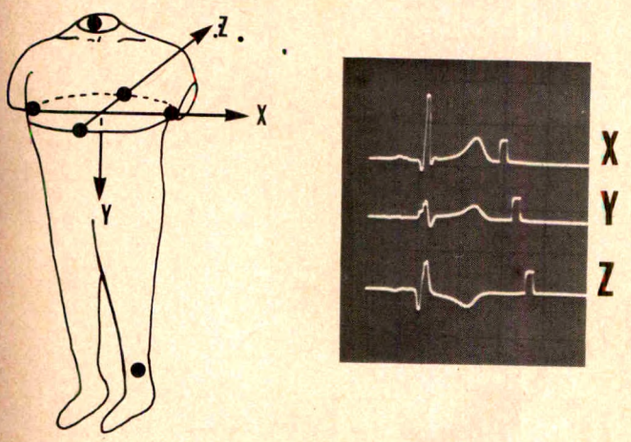

FIGURE 1. Left, schematic representation of the Frank lead system demonstrating the orientation of the three orthogonal leads: The X axis lead is oriented right to left in the horizontal plane, the Y axis lead is oriented vertically in the frontal plane and the Z axis lead is oriented anteroposteriorly along the line of the intersection of the horizontal and sagittal planes. **Right,** scalar orthogonal electrocardiogram of a normal person. By convention, the Z polarity is reversed when compared with the standard lead V_2, that is, anterior forces are inscribed as Q waves and posterior forces as R waves.

Methods

Patients: The study population consisted of 56 consecutive men, mean age 52, who presented for evaluation of chest pain. An orthogonal Frank electrocardiogram (Fig. 1) was obtained in each patient 24 to 48 hours before catheterization and stored on magnetic tape.

Angiography: All patients underwent biplane (30° right anterior oblique and 60° left anterior oblique) ventriculography and coronary angiography. The ejection fraction was calculated according to the length-area method of Dodge.[10] An electrocardiogram was projected simultaneously on the cine film to assure the selection of sinus beats for these measurements. Postextrasystolic beats were not used for determination of ejection fraction.

Orthogonal electrocardiography: The Z lead of the Frank orthogonal electrocardiogram is by convention[6] recorded with a polarity reversed in comparison with that of lead V_2 of the standard 12 lead scalar electrocardiogram. Thus, the Q wave in the orthogonal Z lead (Frank) represents anterior forces and corresponds to the R wave in lead V_2 of the standard electrocardiogram whereas the R wave of the Z lead of the Frank electrocardiogram is comparable with the S wave in lead V_2. As previously described,[7] a Control Data Corporation computer was used to evaluate the electrocardiographic tracings. To eliminate beat to beat variation an average of five to six instrumental measurements were used to establish the required diagnostic criteria. Computer electrocardiographic diagnoses were obtained using multivariate analysis based on a reference data pool of more than 28,000 tracings.[8] Diagnoses were reported in percent probability.[9] A myocardial infarction was diagnosed only when the probability was in excess of 50 percent.

Patients were excluded only if the computer diagnosis indicated a conduction defect or left ventricular hypertrophy, or both. On this basis one patient with left bundle branch block and three with left ventricular hypertrophy were eliminated, leaving a final study group of 52 patients.

In the following determinations and correlations the nomenclature of the Frank electrocardiogram has been used, thus labeling the forces in the Frank Z lead opposite to the standard 12 lead electrocardiogram.[6] To clarify this for the reader accustomed to the standard electrocardiogram a normal orthogonal (Frank) electrocardiogram is shown in Figure 1.

Statistical evaluation was performed with Student's t test, and linear multivariate regression analyses were made according to standard formulas.[11]

TABLE I

Relation of Q and R Forces to Left Ventricular Ejection Fraction (EF)

Linear Correlations (r)		
Q Amplitude With EF	R Amplitude With EF	Total Voltage With EF
Q_x 0.21	R_x 0.59*	QR_x 0.40*
Q_y 0.08	R_y 0.41*	QR_y 0.45*
Q_z 0.51*	R_z 0.46*	QR_z 0.01
$R_x + R_y + Q_z$ 0.78*; $QR_x + QR_y + QR_z$ 0.56*		

Multiple Correlations (r)
R_x, R_y, Q_z 0.80*
R_x, R_y, R_z
Q_x, Q_y, Q_z 0.82*

* ≐ $P < 0.01$.
r = correlation coefficient.

Results

Relation of R and Q amplitudes to ejection fraction: Regression analysis results showing the relation of R waves in leads X, Y, Z (Rx, Ry, Rz) and Q waves in leads X, Y and Z (Qx, Qy, Qz) to the ejection fraction are listed in Table I. A statistically significant correlation ($P < 0.01$) existed between the R waves in the X, Y and Z leads and Q wave in the Z lead. By comparison, the correlation of the Q wave amplitude with ejection fraction was not significant in the X and Y axis leads, whereas the Rz wave did correlate with ejection fraction ($r = 0.46$, $P < 0.01$). A simple arithmetic summation of the three forces Rx + Ry + Qz (ΣR) improved the correlation coefficient to 0.78. A significant correlation also existed between total voltage, that is, sum of the Q and R wave amplitudes in the X and Y leads and ejection fraction as well as the arithmetic sum of (Qx + Rx) + (Qy + Ry) + (Qz + Rz), but the latter was less impressive than ΣR.

Multivariate correlation was performed wherein the Q and R wave amplitudes of the X, Y and Z leads were considered independent variables and ejection fraction the dependent variable. The resulting correlation coefficient for Rx, Ry, Qz was 0.80, slightly above the value calculated for the arithmetic sum of these forces.

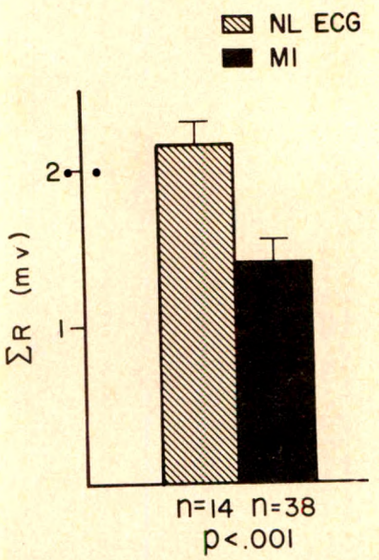

FIGURE 2. Comparison of the arithmetic sum ± standard error of Rx + Ry + Qz (ΣR) of 14 patients with a normal electrocardiogram (NL ECG) **(hatched bar)** and 38 patients with the electrocardiographic diagnosis of myocardial infarction (MI) **(solid bar).** p = probability.

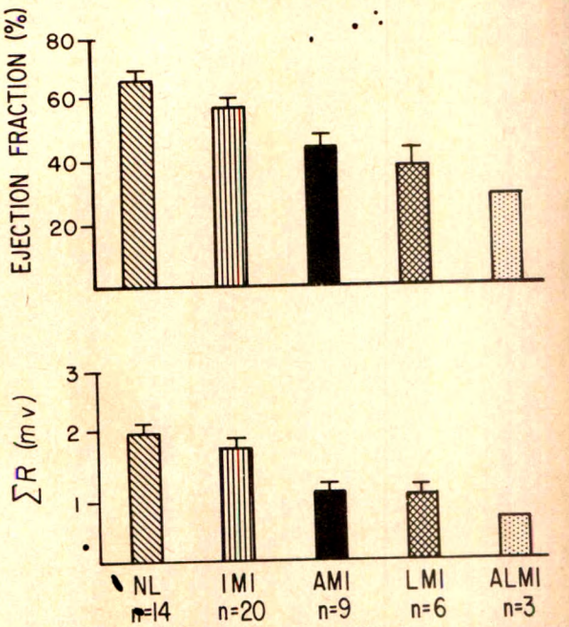

FIGURE 3. Top, ejection fraction in the 52 patients classified according to infarct location. There was a progressive decrease in mean ejection fraction from normal (NL) persons to patients with inferior (I), anterior (A), lateral (L) and anterolateral (AL) myocardial infarction (MI). **Bottom,** ΣR (Rx + Ry + Qz) shows a similar decrease within the same patient subgroups. n = number of patients.

The addition of Qx, Qy and Rz to a total of six independent variables in the multiple correlation minimally increased this correlation coefficient to 0.82.

Infarction versus normal group: The sum of the amplitudes Rx + Ry + Qz (ΣR) in millivolts (mv) was compared in a group of subjects with a normal electrocardiogram and a group with myocardial infarction (Fig. 2). The group with infarction had a significantly lower ΣR (1.46 ± 0.34 mv) than the normal group (2.13 ± 0.5 mv) (P <0.001).

Infarct location also showed an association with ejection fraction (Fig. 3, top). The patients with electrocardiographic changes of anterolateral infarction had a significantly lower ejection fraction than those with inferior myocardial infarction, who in turn had a mean ejection fraction significantly lower than that of the normal group. A similar association could be shown for ΣR and infarct location (Fig. 3, bottom). In comparison with the normal population there was a progressive decrease in ΣR as one proceeded to examine patients with inferior, anterior, lateral and combined infarcts. When ΣR within each infarct group was related to ejection fraction there was a statistically significant correlation with ΣR in all infarct groups (Table II).

Regression relation with ΣR as a predictor of ejection fraction: The 52 values for ΣR (Rx + Ry + Qz) were related to ejection fraction (Fig. 4). The resulting formula for the regression line was ejection fraction percent = 24.6 + 18.7 (Rx + Ry + Qz) (mv); r = 0.78. The use of this regression relation with ΣR as a screening test was evaluated for its capacity to predict an ejection fraction greater or less than 50 percent. Fourteen of 16 patients with an ejection fraction of less than 50 percent had an ΣR value of less than 1.2 mv, whereas 2 had an ΣR value of more than 1.2 mv. In contrast, two of 36 patients with an ejection fraction greater than 50 percent had an ΣR value of less than 1.2 mv. These values indicate a sensitivity rate of 88 percent, a specificity rate of 94 percent and an accuracy rate of 92 percent in predicting an ejection fraction above or below 50 percent.

Discussion

The ejection fraction as a measure of left ventricular pump function is generally considered an important prognostic index in coronary artery disease, whether the patients are treated medically or surgically. Whereas systolic time intervals,[12] echocardiography[13] and radionuclide left ventricular angiography have received considerable attention for their ability to predict ejection fraction,[14] little heed has been paid to the information derivable from the inexpensive readily available technique of electrocardiography.

Previous studies on correlation of electrocardiogram and ejection fraction: Both experimental work and clinical observations using epicardial and precordial

TABLE II

Relation of ΣR (Rx + Ry + Qz) With Ejection Fraction in Each Group of Patients With Infarction

Infarct Location	Cases (no.)	r	P
Inferior wall	20	0.48	<0.05
Anterior wall	9	0.82	<0.01
Lateral wall	6	0.93	<0.01

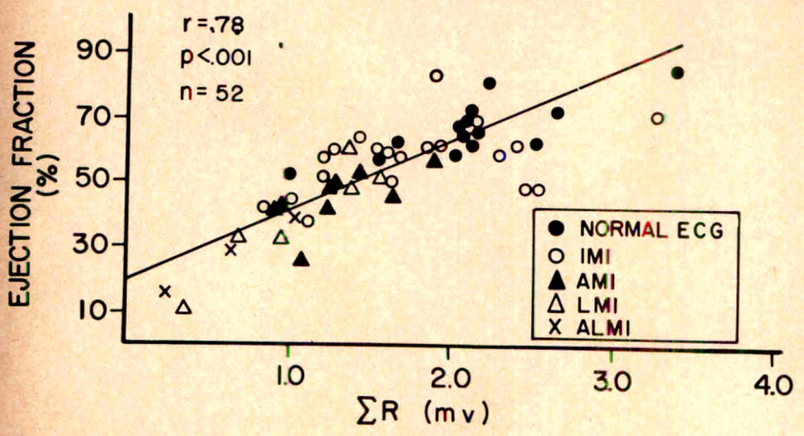

FIGURE 4. Correlation of ejection fraction with ΣR (Rx + Ry + Qz) for each patient studied. The **solid circles** represent a normal electrocardiogram (ECG); the myocardial infarcts are coded by location as indicated in the inset. p = probability; other abbreviations as in Figure 3. Formula for regression line: ejection fraction (percent) = 24.6 + 18.7 (ΣR) mv.

maps[3–5] have shown that Q waves and R waves correlate with the extent of myocardial necrosis[15,16] as assessed with histologic examination and creatine kinase enzyme studies.[17] Previously there was also documentation that the amount of muscle necrosis correlated well with the ejection fraction as a measure of left ventricular function.[18] Whereas most of the experimental studies have been performed in the acute stage of infarction, many clinical surveys[19–23] have been extended to the chronic stage, when the infarcted area has been transformed into a noncontractile segment of the left ventricular wall.

Several recent studies have indicated a relation between the standard 12 lead electrocardiogram and left ventricular function.[1–5] Usually the number of Q waves,[4] their amplitude[1,24] and duration[25] have been analyzed for a relation to left ventricular function. In a recent report, Askenazi et al.[5] showed significant correlation between the sum of unipolar R wave amplitudes in leads I, aVL and V_1 to V_6 of the 12 lead scalar electrocardiogram with ejection fraction; this relation improved when the augmented ejection fraction obtained from postextrasystolic beats was evaluated.

R wave in orthogonal leads as an index of left ventricular ejection fraction: Because much previous work has been limited to information derived from the anterior cardiac wall that is easily accessible to mapping in the open chest dog model or with use of a precordial set of 6 to 35 electrodes,[4,5] it appeared appropriate to use an orthogonal electrocardiographic system that provided an unbiased assessment of the QRS voltage in the frontal, horizontal and sagittal planes.[6–9] This approach allowed us to include patients with inferior infarction in this study. In the scalar 12 lead electrocardiogram inferior infarction cannot be evaluated in a way comparable with anterolateral infarction because leads II, III and aVF are the only three denominators for location of an inferior infarct whereas 8 leads are available to render measurements pertaining to anterolateral infarction, that is, leads I, aVL and V_1 to V_6. Our results, based on the Frank orthogonal system, indicate that the R wave is superior to the Q wave as an index of left ventricular ejection fraction in patients evaluated for chest pain. Statistical analysis indicated that the simple arithmetic summation of orthogonal amplitudes Rx + Ry + Qz was an adequate and practical index that had an important linear correlation with ejection fraction. It was improved only slightly by using much more complex and time-consuming multivariate correlations.

The determination of sensitivity, specificity and accuracy of QRS forces as a predictor of ejection fraction serves as a useful and accurate clinical tool for discriminating ejection fractions greater or less than 50 percent. With ΣR (Rx + Ry + Qz) of the orthogonal electrocardiogram alone, regardless of location of infarction or the presence of Q waves, this accuracy rate was 92 percent.

Our results were obtained in men nearly homogeneous in age. A similar study will have to be performed in women because the regression relation might be different because of inherent sexual differences in the electrocardiograms of men and women.[26]

R wave voltage in group with normal electrocardiograms: A wide range of ΣR was also observed in the subgroup of our patients with normal electrocardiographic findings. All patients in our study were evaluated for chest pain, which in most was poorly controlled with medical management. Sixty-five percent of the population with normal electrocardiographic findings proved to have significant coronary artery disease involving at least one vessel: 56 percent had two or more vessels involved. Thus, several patients in this group had an ejection fraction of less than 50 percent with a concomitantly low ΣR. This may be accounted for, in part, by infarction, which reduced R waves but was not recognized in the resting electrocardiogram even with computer technology.

R wave voltage in group with inferior myocardial infarction: The subgroup with inferior myocardial infarction showed a lower correlation coefficient with ejection fraction and a better ejection fraction than the subgroups with infarcts in anterior and lateral locations. Anatomically the right coronary artery supplies less of the left ventricular myocardial mass than does the left anterior descending coronary artery. Occlusion of the right coronary artery may lead to an infarction whose severity is more difficult to grade because less damage

is usually involved. This view is supported by the generally better prognosis of inferior than anterior infarction.[27,28]

Implications: This study independently confirms previous work of others[4,5] who have reported that changes of the QRS complex may be used as an index of left ventricular function. The use of an orthogonal lead system allowed us to expand the area of interest to the inferior wall, whereas many previous studies were restricted to the anterior surface of the heart. Our results indicate that the orthogonal ΣR value (Rx + Ry + Qz) in our patient population is a good indicator of left ventricular function, more accurate in the presence of anterior and lateral wall damage than in inferior infarction. This measurement can be viewed as a simple noninvasive aid in prescreening candidates for coronary surgery among patients with medically treated refractory angina pectoris.

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Effects of Postextrasystolic Potentiation on Systolic Time Intervals

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The changes in systolic time intervals associated with postextrasystolic potentiation were studied in 48 patients whose left ventricular function was categorized angiographically into four groups—normal function (I) and mild (II), moderate (III) and severe (IV) left ventricular dysfunction. Postectopic potentiation in all groups caused a decrease in preejection period/left ventricular ejection time (PEP/LVET) ratio. The greatest potentiation and decreases in PEP/LVET ratio were noted in beats where the difference in compensatory pause and coupling interval (both expressed as percent of basic cycle length [CP percent − CI percent]) exceeded 40. The decrease in the ratio was least in the normal subjects (Group I) and maximal in Group IV patients. The pattern of response of the rate-corrected left ventricular ejection time and preejection period was also different at the four levels of ventricular function. Marked shortening of ejection time with minimal shortening of preejection period occurred in Group I, but in Group IV patients there was marked shortening of preejection period and minimal shortening of ejection time. An intermediate response was seen in Group II and III patients. The amount of shortening of ejection time exceeded that of preejection period in Group II patients; the reverse was true in Group III patients. The group responses differed with a significance of $2P < 0.001$ except when Group II was compared with Group III, when the significance was $2P < 0.025$. Thus, measurement of changes in systolic time intervals associated with postextrasystolic potentiation is of value as a noninvasive means of assessing resting left ventricular function.

Interest in postextrasystolic potentiation has been recently revived, and it has been used during angiography to determine reversible areas of left ventricular dysfunction.[1–3] Measurement of systolic time intervals, an effective noninvasive means of studying ventricular function,[4] allows detection of beat to beat changes of left ventricular performance and is uniquely suited for the study of postectopic potentiation; yet such use has never been studied in detail. Only two previous studies are available, one showing changes in left ventricular ejection time with paired electrical stimulation,[5] the other performed in patients with hypertrophic obstructive cardiomyopathy.[6] In this report we describe the effect of postectopic potentiation on the systolic time intervals during diagnostic cardiac catheterization in a group of patients with different levels of left ventricular function.

Methods

Patients: Forty-eight patients undergoing diagnostic cardiac catheterization were studied before angiography. Systolic time intervals were measured from the external phonocardiogram (200 to 400 hertz), lead II of the electrocardiogram and external carotid pulse tracing with use of a multichannel pressurized-ink direct-writing recorder at a paper speed of 100 mm/sec. The carotid pulse transducer (EMT no. 29) and the recorder had a time constant of more than 2.5

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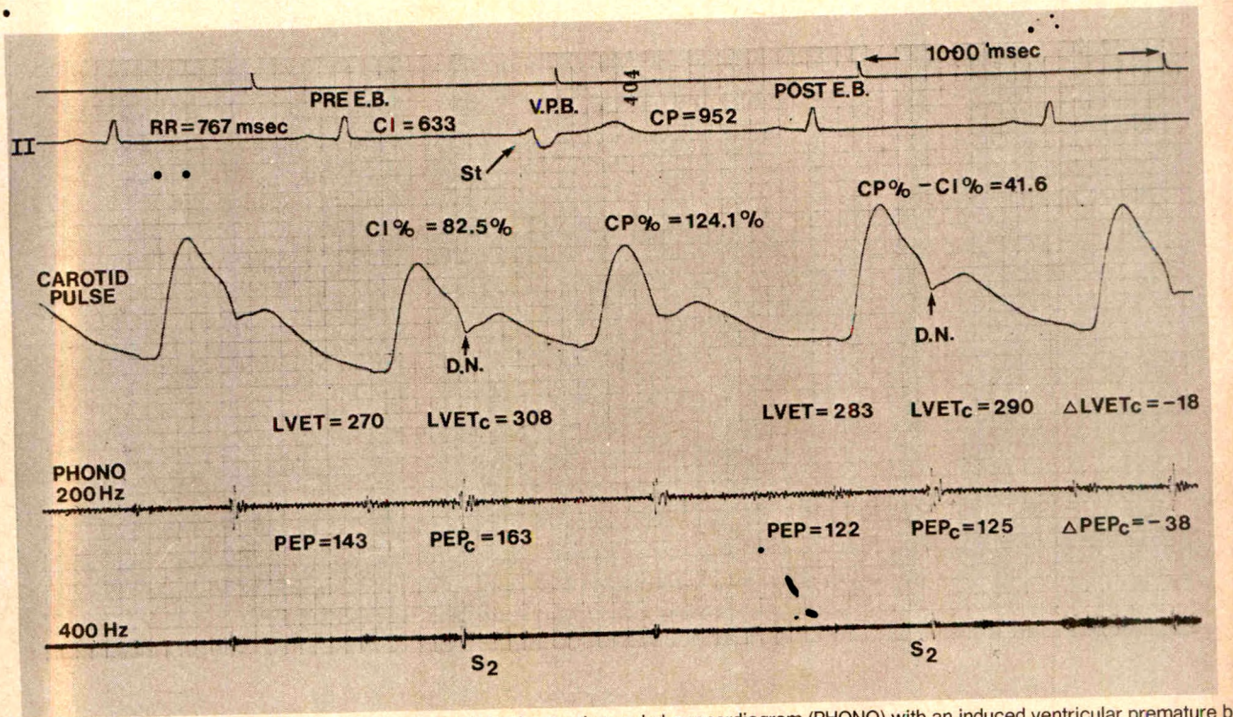

FIGURE 1. Simultaneous lead II electrocardiogram, carotid pulse tracing and phonocardiogram (PHONO) with an induced ventricular premature beat (V.P.B.). The calculated systolic time intervals for the preextrasystolic and the postextrasystolic beats (PRE and POST E.B.) are indicated in milliseconds (msec). The R-R interval (in seconds) of the cycle preceding the preextrasystolic beat is used for the rate correction of that beat. The compensatory pause (CP in seconds) is used as the R-R interval of the first postextrasystolic beat and is used for its rate correction. The coupling interval (CI) and the compensatory pause are expressed as a percent of the basic cycle length (CI% and CP%, respectively). The changes in the rate-corrected left ventricular ejection time ($LVET_c$) and rate-corrected preejection period (PEP_c) are shown as Δ values. All intervals are in msec. D.N. = dicrotic notch; LVET = uncorrected left ventricular ejection time; PEP = uncorrected preejection period; St = stimulus.

seconds. All patients had sinus rhythm. None had cardiac valve disease. Timed single premature ventricular stimulations were produced with varying coupling intervals through an electrode catheter in the right ventricle. At least 10 premature beats were produced with varying coupling intervals in each patient. Because postectopic potentiation has been shown to last for several beats, at least 0.5 minute lapsed between each induced premature beat. Systolic time interval measurements were obtained before and during the periods of induced premature beats. After premature stimulation, left ventriculograms and coronary arteriograms were obtained.

Systolic time interval measurements: Left ventricular ejection time was measured as the interval from the beginning of the upstroke of the carotid pulse to the dicrotic notch. The preejection period was obtained by subtracting the ejection time from the Q-S_2 interval (onset of the QRS complex to the first high frequency component of the second heart sound). The resting measurements were obtained by averaging the data from 10 sinus beats. Systolic time intervals of the sinus beat immediately preceding each premature complex as well as the first four postectopic beats were calculated with the aid of a Numonics digitizer in conjunction with a PDP 11 computer.

The measured intervals were corrected for rate by dividing the observed value by the square root of the preceding cycle length (in seconds).[7] The compensatory pause preceding the first postextrasystolic beat was used as the cycle length for its rate correction. The more popular regression equations obtained from normal subjects for rate correction were not used because these are derived from observations made under resting conditions for heart rates of 50 to 110 beats/min.[8] The compensatory pause representing cycle lengths equivalent to unphysiologically slow heart rates makes the applicability of the normal regression equation doubtful. *All intervals mentioned under Results and Discussion refer to these rate-corrected values.* The changes in the systolic time intervals between the pre- and the postectopic beats were calculated.

The coupling interval and the compensatory pause were expressed as a percent of the preextrasystolic sinus R-R interval (CI percent and CP percent, respectively). It has been known that the more premature the extrasystole and the longer the compensatory pause, the greater is the potentiation.[9] Therefore, the combined effects of the two variables are best expressed when the change is related to the difference between the two variables (CP percent − CI percent). Thus a large difference will indicate a long compensatory pause and a short coupling interval, whereas a small difference will indicate an inadequate compensatory pause and a late coupling interval. Figure 1 shows a sample tracing with calculation of CP percent − CI percent values and changes in rate-corrected individual systolic time intervals.

Left ventricular function (angiography): Left ventriculograms taken in the right anterior oblique projection were used to calculate ejection fraction and percent axis shortening. The recording of electrocardiographic rhythm strips during angiography with markers to indicate the onset and end of each injection facilitated analysis of the ventriculograms. For these quantitative measurements only sinus beats that did not occur immediately after an extrasystole were analyzed. Ejection fraction and percent axis shortening were measured,

as described previously.[10] The normal values for percent axis shortening in our laboratory were similar to those described by others[11] (Fig. 2).

The angiographic criteria for the classification of left ventricular function used in this study are shown in Table I. The 48 patients were separated into four groups: Group I (16 patients), normal left ventricular function; Group II (17 patients), mild dysfunction; Group III (11 patients), moderate dysfunction and Group IV (4 patients), severe dysfunction. The clinical and hemodynamic data of the four patient groups

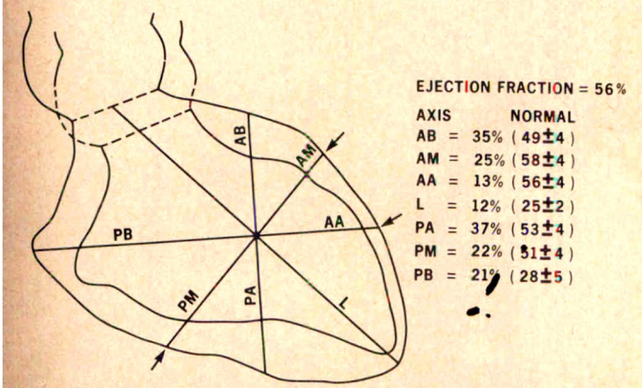

FIGURE 2. Outlines of systolic and diastolic frames of the left ventriculogram in the right anterior oblique projection taken from a patient with mild ventricular dysfunction (Group II) showing a nearly normal ejection fraction with major abnormality in shortening of axes indicated by **arrows.** AA = anteroapical; AB = anterobasal; AM = anteromedial; L = longitudinal; PA = posteroapical; PB = posterobasal; PM = posteromedial.

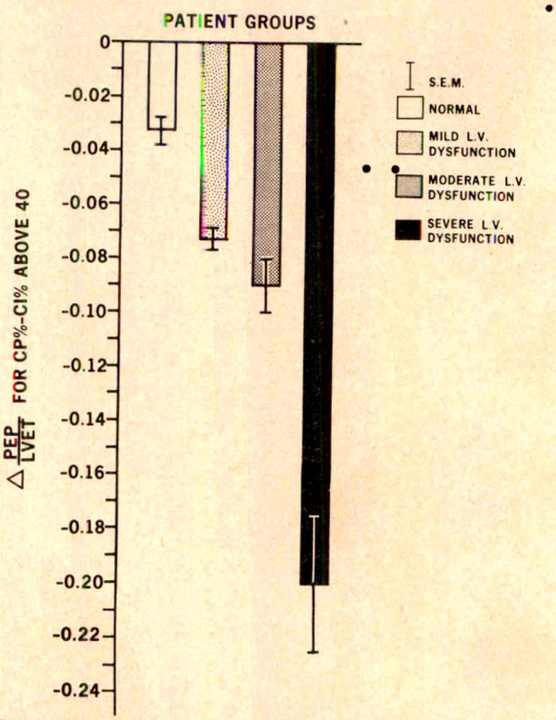

FIGURE 4. Mean change in preejection period/left ventricular ejection time ratio (ΔPEP/LVET) from beats in which the CP% − CI% value exceeded 40 between the resting and the postextrasystolic beat in the four left ventricular (L.V.) function groups. The greater the resting dysfunction, the greater is the potentiation, as shown by the decrease in PEP/LVET ratio. S.E.M. = standard error of the mean.

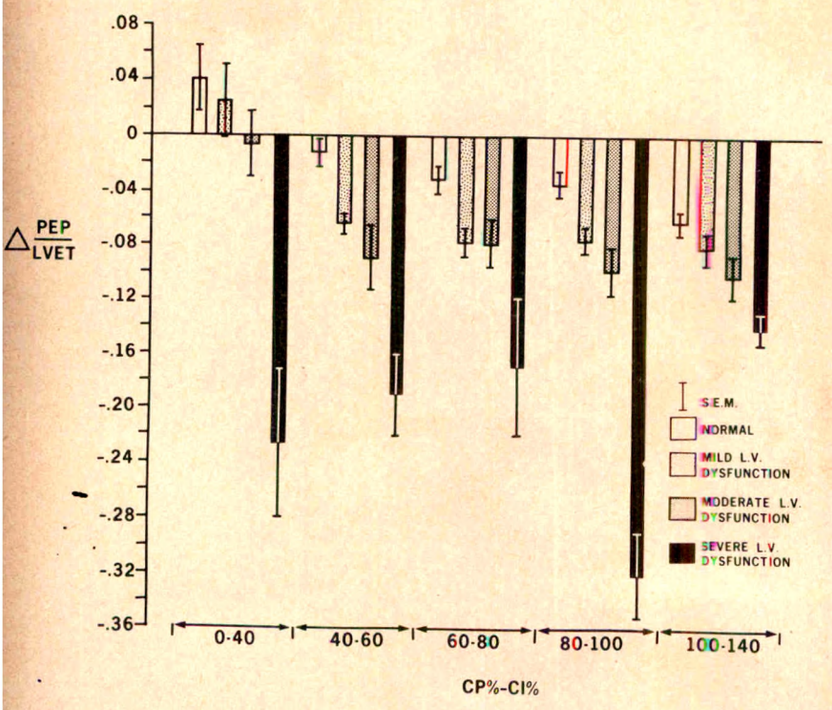

FIGURE 3. Change in preejection period/left ventricular ejection time ratio (ΔPEP/LVET) between the resting and the postectopic beats related to the difference between the compensatory pause and the coupling interval, both expressed as a percent of the basic cycle length (CP% − CI%). A significant decrease in the PEP/LVET ratio is noted in beats where the CP% − CI% value exceeded 40. Beats with a CP% − CI% value less than 40 showed an increase in this ratio in two of the four groups, indicating lack of potentiation. L.V. = left ventricular; S.E.M. = standard error of the mean.

are shown in Table II. A total of 420 observations were made. The induced ventricular premature beats had comparable degrees of prematurity in all four groups of patients. The postectopic changes in systolic time intervals for each group represent the mean of all the observations from that group. The mean postectopic changes in the systolic time intervals were then related to the resting left ventricular function.

Results

Analysis of the First Postextrasystolic Beat

Change in PEP/LVET ratio (ΔPEP/LVET) as related to the compensatory pause and the coupling interval: The change in preejection period/left ventricular ejection time (PEP/LVET) ratio was related to different ranges of difference between compensatory pause and coupling interval, both expressed as percent of the basic cycle length (CP percent − CI percent) (Fig. 3). In all patients potentiation was seen as a decrease in this ratio for all ranges of CP percent − CI percent values greater than 40, indicating adequately long compensatory pauses and relatively short coupling intervals. However, for beats with a CP percent − CI percent value less than 40, this ratio increased in Groups I and II, indicating a probable lack of potentiation in the first postextrasystolic beat. These beats (CP percent − CI percent less than 40) were therefore eliminated from the rest of the study.

Mean change in PEP/LVET ratio (ΔPEP/LVET): The mean change in PEP/LVET ratio from all beats with ranges of CP percent − CI percent values greater than 40 is shown for each patient group in Figure 4 and Table III. In all four groups potentiation is evident

TABLE I

Patient Classification According to Left Ventricular (LV) Function as Assessed With Angiography

Group	Angiographic Classification
I	Normal LV function; EF >60%; normal axis shortening
II	Mild LV dysfunction; EF = 50 to 60% and/or at least two major abnormalities* in axis shortening
III	Moderate LV dysfunction; EF = 30 to 50%
IV	Severe LV dysfunction; EF <30%

* Major abnormality in axis shortening means shortening less than 50 percent of normal.
EF = ejection fraction; LV = left ventricular.

TABLE II

Clinical Data of the Patients Studied

Group	Patients (no.)	Mean Age (yr)	Sex Ratio M/F	Type of Heart Disease	Patients With Cardiomegaly (no.)	Patients With S_3 (no.)	Patients With ECG Evidence of MI (no.)	Resting PEP/LVET (m ± SEM)	LVEDP (m ± SEM)	CI (m ± SEM)
I	16	49	12/4	CAD 11; AP 5	None	None	1	0.33 ± 0.02	11 ± 1.3	3.56 ± 0.24
II	17	47	12/5	CAD 13; AP 4	None	None	7	0.38 ± 0.02	13 ± 1.6	3.33 ± 0.22
III	11	47	10/1	CAD 10; C 1	6	1	6	0.41 ± 0.04	16 ± 2.4	3.12 ± 0.28
IV	4	50	3/1	CAD 3; C 1	4	4	3	0.72 ± 0.06	30 ± 0.7	2.94 ± 0.36

AP = atypical chest pain; C = cardiomyopathy (congestive); CAD = coronary artery disease; CI = cardiac index (liters/min per m^2); ECG = electrocardiographic; LVEDP = left ventricular end-diastolic pressure (mm Hg); m ± SEM = mean ± standard error of the mean; MI = myocardial infarction; S_3 = ventricular diastolic gallop.

TABLE III

Postextrasystolic Changes in Systolic Time Intervals in Different Left Ventricular (LV) Function Groups for CP% − CI% Values Greater Than 40 (mean ± standard error of the mean)

	Group I	Group II	Group III	Group IV
ΔPEP/LVET	−0.033 ± 0.005	−0.073 ± 0.004	−0.090 ± 0.010	−0.202 ± 0.026
$\Delta LVET_c$ (msec)	−59.5 ± 2.0	−43.0 ± 1.6	−38.0 ± 2.0	−14.0 ± 4.5
ΔPEP_c (msec)	−31.2 ± 1.3	−36.4 ± 1.1	−41.0 ± 3.0	−60.0 ± 4.3
$\Delta LVET_c - \Delta PEP_c$	−29.1 ± 2.3	−6.7 ± 2.1	3.0 ± 4.0	47.0 ± 6.4

CI% = coupling interval and CP% = compensatory pause both expressed as percent of R-R interval of the preextrasystolic sinus cycle; $\Delta LVET_c$ = change in the rate-corrected left ventricular ejection time; ΔPEP_c = change in the rate-corrected preejection period.

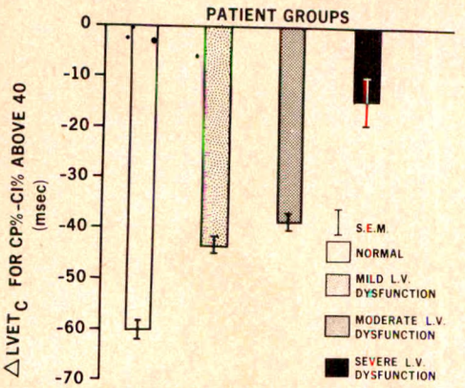

FIGURE 5. The mean change in corrected left ventricular ejection time ($\Delta LVET_c$) between the resting and the postextrasystolic beats where the CP% − CI% value exceeded 40 is shown for different left ventricular (L.V.) function groups. Marked shortening in $LVET_c$ was noted in patients with normal function, with a stepwise decrease in $LVET_c$ shortening with increasing ventricular dysfunction. S.E.M. = standard error of the mean.

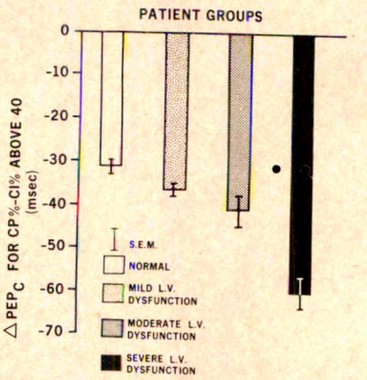

FIGURE 6. Mean change in corrected preejection period (ΔPEP_c) between the resting and the postextrasystolic beats where the CP% − CI% value exceeded 40 is shown for the four left ventricular (L.V.) function groups. The shortening of PEP_c is maximal in patients with severe dysfunction and least in patients with normal ventricular function.

as a decrease in this ratio, the maximal decrease occurring in Group IV (severe dysfunction). There is a progressive increase in the amount of potentiation as the ventricular function decreases. Minimal change in this ratio was observed in Group I patients (normal ventricular function).

Change in rate-corrected Q-S_2 interval: Although total electromechanical systole shortened in all four groups, the mean change differed little among groups.

Change in rate-corrected left ventricular ejection time (Fig. 5, Table III): The ejection time shortened in the postectopic beat in all four patient groups. Shortening was maximal (−59.5 ± 2.0 msec [mean ± standard error of the mean]) in Group I patients (normal function) and least (−14 ± 4.5 msec) in Group IV patients (severe dysfunction). In fact, one patient in this group who had an ejection fraction of 14 percent had prolongation of ejection time. In Group II and III patients (mild and moderate dysfunction, respectively) the shortening was moderate and slightly greater in Group II than in Group III.

Change in rate-corrected preejection period (Fig. 6, Table III): In contrast to the changes in ejection time, maximal shortening of preejection period occurred in Group IV patients (−60 ± 4.2 msec). A progressive decrease in shortening was noted with increasing ventricular function. Thus, the least shortening (−31 ± 1.3 msec) was seen in Group I patients (normal function).

Relation of the change in rate-corrected ejection time to the change in the rate-corrected preejection period in different functional groups: The mean change in ejection time and preejection period for different CP percent − CI percent ranges in all four groups of patients is plotted in Figure 7. The algebraic difference between the two ($\Delta LVET_c - \Delta PEP_c$ in Fig. 7), which is also plotted, further depicts this relation. Different ranges of CP percent − CI percent values indicate varying combinations of compensatory pauses and coupling intervals, the lower ranges (40 to 60) being less ideal for potentiation than the high ranges (100 or more).

In Group I the shortening of ejection time was approximately twice the amount of shortening of the preejection period. The algebraic difference between the two ($\Delta LVET_c - \Delta PEP_c$, Fig. 7) was in the negative range, indicating a greater change in the ejection time than in the preejection period. In Group II patients (mild dysfunction) changes in ejection time and preejection period were equal for low CP percent − CI percent ranges. For higher ranges, the two curves diverged, the shortening of ejection time being greater than that of the preejection period.

In Group III (moderate dysfunction) the first reversal was seen: The algebraic difference ($\Delta LVET_c - \Delta PEP_c$, Fig. 7) became positive for lower ranges of CP percent − CI percent values (40 to 60); that is, the change in preejection period was greater than the change in ejection time. In the mid ranges (60 to 100) the two intervals shortened by relatively the same amount, whereas in the higher ranges, the change in ejection time exceeded the change in preejection period. The patients in Group IV (severe dysfunction) showed a reversal of relation between changes in ejection time and preejection period in all CP percent − CI percent ranges, thus demonstrating a very positive value for the $\Delta LVET_c - \Delta PEP_c$ difference.

The relative changes in ejection time and preejection period were also evident in the *mean* difference between the two intervals in each of the four groups (Fig. 8, Table III). In Group I and II patients, the difference was in the negative range because the change in ejection time exceeded the change in preejection period, whereas in Groups III and IV, this difference was positive. The gradations of negativity and positivity reflected the resting ventricular function.

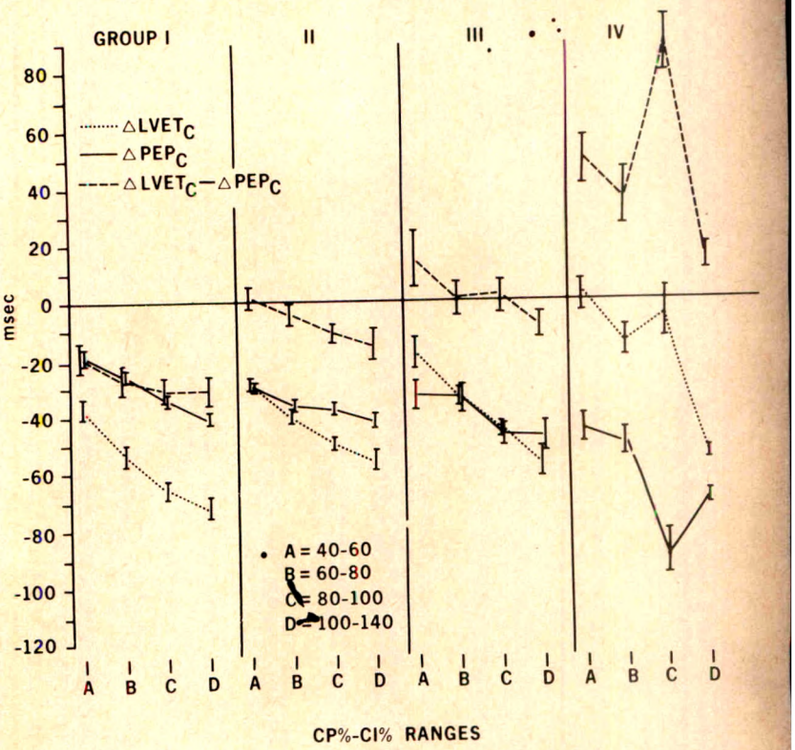

FIGURE 7. The mean change in corrected left ventricular ejection time ($\Delta LVET_c$) and corrected preejection period (ΔPEP_c) as well as the algebraic difference between the two ($\Delta LVET_c - \Delta PEP_c$) for each ventricular function group for different ranges of CP% — CI% (A,B,C,D). See text.

Comparison of the mean change in systolic time intervals among different grades of ventricular function: The results were analyzed applying an analysis of variance to each of the four variables (Table III). The variance ratios were large and clearly different among groups. The true significance level was considerably lower than the value 0.001. Because the four groups were selected a priori, we considered it legitimate to compare Group II with Group III and values in Groups I and IV with the mean values in Groups II and III. It was found that Groups II and III differed significantly only in the algebraic difference between the change in ejection time and the change in preejection period ($\Delta LVET_c - \Delta PEP_c$, Table IV). Groups I and IV differed (in opposite directions) very markedly from Groups II and III. In fact, the differences were so great that they would be highly significant even if the comparisons had been made between groups selected "a posteriori."

Comparison of resting systolic time intervals and postectopic responses in individual patients: Two patients in Group I had an abnormal resting PEP/LVET ratio (greater than 0.42). Furthermore, 21 patients in Groups II and III with mild or moderate left ventricular dysfunction had a resting PEP/LVET ratio in the normal range (13 in Group II and 8 in Group III). Thus, 23 of the total of 48 patients (48 percent) had a resting PEP/LVET ratio inconsistent with the level of ventricular function as assessed with angiography. In contrast, when postectopic responses of individual patients were related to the mean of the group to which they belonged, only 12 of 48 patients (25 percent) formed exceptions, and in all cases these were due to

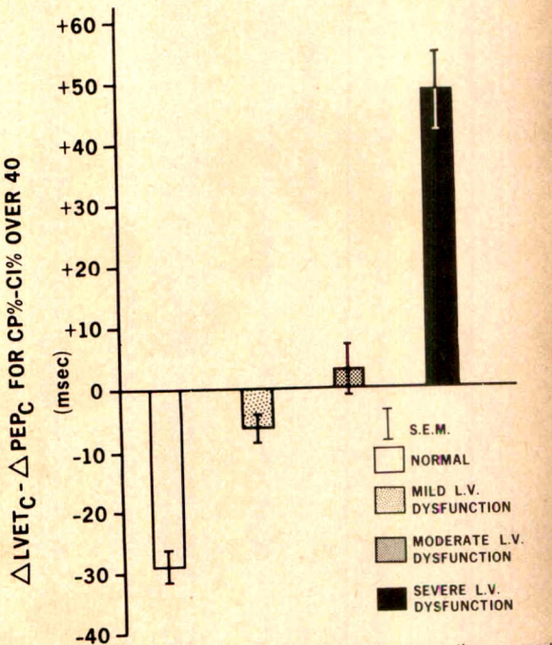

FIGURE 8. Mean of the algebraic difference between the corrected ejection time and corrected preejection period ($\Delta LVET_c - \Delta PEP_c$) observed in different left ventricular (L.V.) function groups from beats with a CP% — CI% value exceeding 40. Marked shortening in $LVET_c$ and little shortening of PEP_c in patients with normal function is reflected in the very negative values (−29 msec) whereas the opposite changes in $LVET_c$ and PEP_c in patients with severe dysfunction result in high positive values (47 msec). The mean difference is negative in patients with mild dysfunction but positive in those with moderate dysfunction although the absolute values are small. S.E.M. = standard error of the mean.

TABLE IV

Statistical Analysis of the Difference Between Mean Changes in Systolic Time Intervals in Table III

	Group I vs II (2P)	Group I vs 1/2 (II + III) (2P)	Group I vs IV (2P)	Group II vs III (2P)	Group 1/2 (II + III) vs IV (2P)	Group III vs IV (2P)
ΔPEP/LVET	<0.001	<0.001	<0.001	NS	<0.001	<0.001
$\Delta LVET_c$	<0.001	<0.001	<0.001	NS	<0.001	<0.001
ΔPEP_c	<0.005	<0.001	<0.001	NS	<0.001	<0.001
$\Delta LVET_c - \Delta PEP_c$	<0.001	<0.001	<0.001	<0.025	<0.001	<0.001

$\Delta LVET_c$ = change in the rate-corrected left ventricular ejection time; NS = not significant; *P* = probability; ΔPEP_c = change in the rate-corrected preejection period.

variability inherent in biologic data. Two of 16 patients in Group I had a response similar to that of Group II. Of 17 Group II patients, 2 had a Group I response and 5 had a Group III response. Of 11 Group III patients, 2 had a Group II response while 1 had a Group IV response.

Analysis of the Second, Third and Fourth Postectopic Beats

The second, third and fourth postectopic beats demonstrated relative lack of potentiation as measured with systolic time intervals. In fact, in Group IV patients an alternans effect was demonstrated, with depression of left ventricular function in the second postectopic beat as shown by a significant increase in the PEP/LVET ratio (mean ΔPEP/LVET = +0.08). This returned to preectopic beat level by the fourth beat. This depression was noted to a lesser degree in Group III patients (mean ΔPEP/LVET = +0.03). By contrast, systolic time intervals in Group I and II patients returned to preectopic levels by the second beat (Table V). These observations relative to PEP/LVET ratio were also seen in the individual systolic time intervals.

Discussion

That the beat following an extrasystole shows greater than normal force of contraction has long been known.[9,12–19] The phenomenon was first described by Langendorff,[12,13] who called it "postextrasystolic compensation" because the increased force of the postectopic beat was thought to compensate for the weakness of the premature beat. Although many years later Hoffman et al.[17] renamed it "postextrasystolic potentiation," some of the crucial work with regard to the basic properties of the phenomenon were carried out around the turn of the century in isolated heart muscle preparations.[9,12–16,18,19] Woodworth[9] in particular demonstrated clearly the strength of the postectopic beat to be "closely dependent on the earliness of the extra contraction and somewhat loosely dependent on the length of the pause" and observed that the "actual stimulating effect persists on the average for about eight subsequent beats." Working with isolated perfused apical muscle preparations, he showed the potentiation to be independent of both filling and neurogenic influences. The studies of Hoffman et al.[17] and others[20–23] confirmed and extended these observations to ventricles contracting isovolumically. Although subsequently the phenomenon has been investigated by many workers,[1–3,5,6,24–29] examination of its effects on systolic time intervals has been somewhat neglected. Braunwald et al.[5] did demonstrate the shortening of ejection time to accompany potentiation in nine patients studied with paired electrical stimulation. Our study examines for the first time the effects of postectopic potentiation on all aspects of the systolic time intervals, as well as relating the findings to ventricular function as assessed with angiography.

Our observations confirm the previously known facts that postectopic potentiation is inversely related to the coupling interval and is dependent on the presence of an adequate compensatory pause that should be in excess of the basic R-R interval. Because the potentiation is best studied by combining the independent effects of the two variables, we expressed both the compensatory pause (CP) and the coupling interval (CI) as a percent of the basic R-R interval and calculated the difference. The larger the difference between CP percent and CI

TABLE V

Change in PEP/LVET Ratio Between the Preectopic Sinus Beat and the First Four Postextrasystolic Beats in the Four Patient Groups (mean ± standard error of the mean)

Group	Postextrasystolic Beats 1st	2nd	3rd	4th
I	−0.03 ± 0.01	0.02 ± 0.01	0.00 ± 0.01	0.00 ± 0.01
II	−0.07 ± 0.01	0.02 ± 0.01	0.00 ± 0.01	0.02± 0.01
III	−0.09 ± 0.01	0.03 ± 0.01	0.01 ± 0.01	0.06 ± 0.03
IV	−0.20 ± 0.03	0.08 ± 0.02	−0.02 ± 0.02	0.04 ± 0.02

percent, the shorter will be the coupling interval, the longer the compensatory pause and the greater the potentiation. Using this observation to help eliminate beats with inadequate compensatory pause, we found that beats with CP percent − CI percent ranges greater than 40 adequately demonstrated potentiation (Fig. 3).

Postectopic potentiation correlated with level of ventricular function: Postectopic potentiation was evident in all patients, as shown by a decrease in the resting preejection period/left ventricular ejection time (PEP/LVET) ratio. However, the amount of decrease was maximal in patients with severe ventricular dysfunction and minimal in those with normal ventricular function. These data are in agreement with previously noted observations that potentiation is most impressive when myocardial performance is severely compromised.[26]

Although there was a progressive increment in the decrease of PEP/LVET ratio from normal function to severe dysfunction, the pattern of response of the rate-corrected components of systolic time interval (ejection time and preejection period) was different at different levels of ventricular function (Fig. 5 and 6, Table III). In patients with normal left ventricular function marked shortening of ejection time occurred with only minimal shortening in preejection period. The order of shortening of ejection time was similar to that described by Braunwald et al.[5] Patients with severe ventricular dysfunction, on the other hand, had significant shortening of preejection period with very little shortening in ejection time. The responses in patients with mild and moderate left ventricular dysfunction were intermediate. With mild dysfunction the change in ejection time exceeded that of the preejection period, whereas with moderate dysfunction the change in the preejection period exceeded the change in ejection time. The relation of the two variables is best expressed by their algebraic difference ($\Delta LVET_c - \Delta PEP_c$) (Fig. 8, Table III). This difference was very negative in patients with normal ventricular function and very positive in those with severe dysfunction. It was mildly negative and mildly positive, respectively, in patients with mild and moderate dysfunction. Thus, the pattern of response in the first postextrasystolic beat seems to be related to the degree of resting left ventricular function. These changes in the systolic time intervals are not artificially induced by the rate correction method, because a similar relation is also seen with changes in PEP/LVET ratio, which are not influenced by rate correction.

Statistical analysis of the mean changes in the systolic time intervals showed a highly significant separation among the different groups, except between those with mild and moderate left ventricular dysfunction. However, latter two groups could be separated by using the algebraic difference ($\Delta LVET_c - \Delta PEP_c$) (Table IV). Thus, the systolic time interval responses of the first postextrasystolic beat appear to be of value in determining resting left ventricular function even when resting systolic time intervals do not reflect the true ventricular function. In fact, 13 patients with mild and 8 patients with moderate left ventricular dysfunction had normal resting intervals although their functional abnormality was demonstrated angiographically as well as with the effects of postectopic potentiation.

The systolic time interval changes of postectopic potentiation do not appear to be significant for second, third and fourth postectopic beats. In fact, the second postectopic beat showed depression of ventricular function in Group IV patients (severe dysfunction) (Table V). The second postectopic beat has been used as a control sinus beat in some angiographic studies of postectopic potentiation.[1] Our observations suggest that this beat may not be representative of the resting left ventricular function in patients with moderate to severe ventricular dysfunction.

Mechanisms of postextrasystolic potentiation effects on systolic time intervals: The mechanism underlying the changes in the systolic time intervals needs to be defined clearly although previous observations help to explain the findings.[5,24,26,27,29] The marked shortening in ejection time noted by Braunwald et al.[5] was related to an increased mean systolic ejection rate, and the potentiation was accompanied by an increase in the rate of rise of intraventricular pressure (dP/dt). Although Beck et al.,[29] in their studies on postextrasystolic ventricular pressure responses in patients with heart failure, demonstrated only a modest rise in dP/dt accompanied by a significant increase in end-diastolic pressure, others[24,27] have shown a marked rise. In all our patients there was shortening of the preejection period reflecting the increased contractility accompanying potentiation. An increase in the velocity of ejection in the postectopic beat will tend to shorten the ejection time whereas an increase in stroke volume due to the compensatory pause will tend to lengthen it. The net effect on the ejection time will depend on which factor dominates. In patients with normal ventricular function, the effect of an increased rate of ejection may overcome the opposing effect of increased stroke volume thereby causing a marked shortening of ejection time. On the other hand, patients with severe left ventricular dysfunction are unable to shorten the ejection time significantly, despite the striking potentiation as evidenced by the marked shortening of the preejection period. In these patients, the increment in stroke volume may be larger because of their large resting end-diastolic volume. Although the rate of ejection may also be increased, it may not overcome the effect of the increased stroke volume, thus resulting in a net effect of only minimal shortening of the ejection time.

Clinical applications of findings: (1) Postectopic potentiation broadens the use of systolic time intervals as a noninvasive means of assessing left ventricular function in patients with spontaneous ventricular premature beats. Furthermore, effective and safe means of mechanically stimulating the heart externally have been recently developed and can be used to produce premature beats.[30] Thus in the future it may be possible to assess ventricular function noninvasively using postectopic potentiation.

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(2) In patients undergoing cardiac catheterization, ventricular premature beats can be induced electrically or mechanically, thus providing an additional means of assessing ventricular function.

(3) Because postectopic potentiation is a form of positive inotropism, the effects of other inotropic agents, such as digitalis and sympathomimetic drugs, on systolic time intervals may have a similar application. Thus, such agents might be used not only to assess drug response but also to assess resting ventricular function.

(4) In left bundle branch block, in which the preejection period as well as the PEP/LVET ratio are of little use, this method, which measures the change in systolic time intervals between the pre- and postectopic beats, may be of value because an abnormal sequence of excitation is present in both, thus canceling out its effects. In fact, preliminary observations in 10 patients (5 studied with angiography) suggest this to be true.

(5) For similar reasons the method could be of value in patients with sympathetic overactivity, which tends to normalize resting systolic time intervals and mask changes of left ventricular dysfunction. Patients with acute myocardial infarction, who very commonly have ventricular premature beats,[31] would be one example.

(6) If the improvement in angiographic ejection fraction in the postextrasystolic beat is an indicator of reversibility of left ventricular dysfunction,[1–3] it is logical to assume that such improvement may have a bearing on "postectopic changes in systolic time intervals." However, this correlation remains to be proved.

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The U Wave and Aberrant Intraventricular Conduction

Further Evidence for the Purkinje Repolarization Theory on Genesis of the U Wave

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The Purkinje system repolarization theory on the genesis of the U wave was tested by correlating the incidence of aberrancy of atrial premature systoles with the timing of the U wave and other measurements in 126 electrocardiograms selected from 6,000 records. Coupling (R_s-R_p) intervals were measured from the onset of the QRS complex of a sinus (s) beat to that of the premature (p) beat, and 149 different R_s-R_p intervals were studied. Criteria used for diagnosing aberrancy were significant changes in the QRS amplitude and significant alterations in the QRS contour. The incidence of aberrancy was plotted against (1) the R_s-R_p interval; (2) the ratio between the R_s-R_p and R_s-R_s intervals (the basic cycle length); (3) the ratio between P_s-P_p (the interval from a sinus P wave to a premature P wave) and P_s-P_s (the sinus cycle length); (4) the interval from the end of the preceding T wave to the premature QRS complex (T-R_p interval); (5) the interval from the apex of the U wave of the sinus beat to the premature QRS complex (aU-R_p); and (6) the interval from the end of the preceding U wave to the premature QRS complex (eU-R_p). As expected, a decrease in either of these values tended to increase the incidence of aberrancy. However, smooth S-shaped curves were noted with aU-R_p and eU-R_p intervals only. The correlation was much poorer with the other four measurements. Aberrancy with a typical right or left bundle branch block pattern was observed only when the premature QRS complex occurred before the apex of the U wave, the left bundle branch block pattern occurring with greater prematurity. It is concluded that the U wave most likely represents phase 3 repolarization of the Purkinje system, and propagation of supraventricular impulses during this period is the cause of aberrant ventricular conduction.

The term aberrant intraventricular conduction is applied when a supraventricular impulse (an impulse originating above the so-called bifurcation of the His bundle) is accompanied by an abnormal spread of ventricular excitation compared with the excitation pattern during the basic rhythm (usually sinus rhythm, but there may be other mechanisms including atrial fibrillation).[1] This condition most commonly results from a sudden shortening of the cardiac cycle[1–3] although prolongation of cycle length and several other factors may also cause such QRS alterations.[4–6] On the basis of various electrophysiologic studies, it is now widely believed that aberrant conduction of supraventricular premature systoles is caused by the arrival of those early impulses in the His-Purkinje system before this system completely recovers its excitability from a preceding depolarization.[7–9] In terms of transmembrane potentials, encroachment of phase 3 repolarization of Purkinje fibers with resultant conduction delay or block in certain fascicles or their ramifications would produce an abnormal QRS contour.

On the other hand, the U wave is the only electrocardiographic wave form whose genesis remains controversial.[10] However, several clinical

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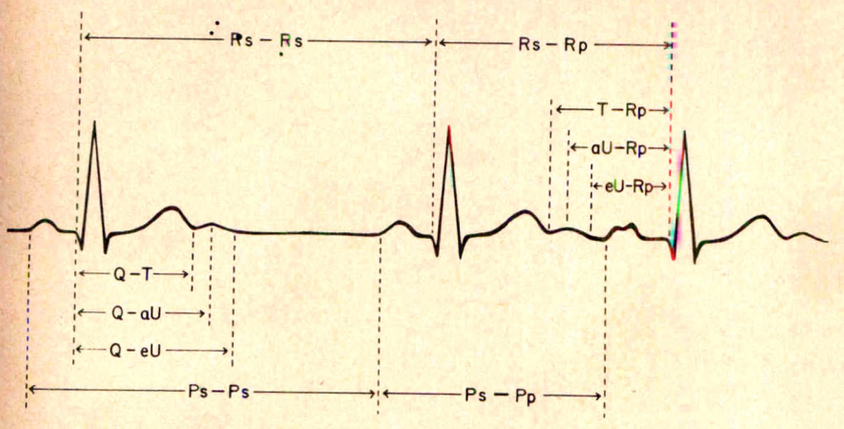

FIGURE 1. Diagram explaining the methods of measuring various time intervals.

and experimental observations led us to suggest that the U wave probably represents phase 3 repolarization of the Purkinje system.[11–13] If this hypothesis is correct, the occurrence of aberrantly conducted supraventricular premature beats should depend on their time of appearance with respect to the U wave. The present electrocardiographic study was designed to test this assumption.

It is possible to differentiate atrioventricular (A-V) junctional premature systoles from their atrial counterparts in a majority of instances by studying the P wave contour and the P-R interval as long as their QRS complex is identical to that of the sinus beats with a normal QRS duration. Once intraventricular conduction becomes aberrant, A-V junctional origin of these premature beats (or escape beats) can no longer be identified with certainty from clinical electrocardiograms alone because impulse formation in the proximal portion of a bundle branch or a fascicle immediately below the bifurcation of the His bundle could show similar QRS deformities.[14] Hence, in this study, only atrial premature systoles were used and their aberrancy was correlated with various time intervals with reference to their preceding beats.

Material and Methods

Six thousand consecutive electrocardiograms recorded in the Heart Station of the Fujita Gakuen University Hospital were reviewed for the presence of atrial premature systoles, and 126 tracings showing this arrhythmia were selected for the study. Each record consisted of four sets of three simultaneous leads (I, II, III; aVR, aVL, aVF; V_1, V_2, V_3; and V_4, V_5, V_6). The following intervals were measured to the nearest 0.01 second: (1) the basic sinus cycle length, (2) the coupling interval, and (3) the Q-T, Q-aU and Q-eU intervals of the sinus beats (Fig. 1).

The basic sinus cycle length was determined between the onset of two consecutive QRS complexes of sinus origin (R_s-R_s interval), which equals the interval between two sinus P waves (P_s-P_s interval). When there was sinus arrhythmia, the basic cycle length was measured as the mean R_s-R_s interval, usually in the particular lead set or sets where the premature systoles were observed.

The coupling interval was measured between the onset of the QRS complex of a sinus beat and that of the following premature beat (R_s-R_p interval). In the presence of several premature systoles in a given record, the coupling intervals of all the ectopic beats were determined. When variations in their coupling intervals were less than 0.04 second, only one representative premature systole was chosen, whereas individual premature beats were subjected to analysis if such variations exceeded this range. Thus, a total of 149 atrial premature systoles were studied to calculate percent incidence of aberrancy as related to various measurements.

The Q-T, Q-aU and Q-eU intervals were defined as the intervals from the beginning of the QRS complex to the end of the T wave, to the apex of the U wave (aU) and to the end of the U wave (eU), respectively. These three intervals were usually measured in precordial leads, especially in the leads showing the most prominent U waves, unless there was a significant difference in heart rate between the leads having premature systoles and those precordial leads. The Q-eU intervals were not obtained in 10 instances in which the terminal portion of the U wave was obscured by superimposition of the following P wave, usually in the presence of relatively rapid sinus mechanisms.

From these measurements, the following values were calculated: (1) the ratio between the coupling interval (R_s-R_p interval) and the basic sinus cycle (R_s-R_s interval), (2) the T-R_p interval (interval between the end of the T wave of the preceding sinus beat and the beginning of a premature QRS complex), and (3) the aU-R_p and eU-R_p intervals as measured from the apex and the end of the U wave, respectively, to the onset of a premature QRS complex (Fig. 1).

The presence of aberrant intraventricular conduction was diagnosed in the following manner: Classically, the term aberrant conduction implies significant alterations in the QRS configuration. Here, significant alterations can be defined as one of the following three changes: (1) appearance of a new deflection (Q, R or S) not present in sinus beats, (2) disappearance of a preexistent Q, R or S deflection, or (3) changes in the QRS pattern, for example, from an rS to an RS pattern, even when the QRS duration was not prolonged. One extreme of such changes in contour is the development of a typical right (or left) bundle branch block pattern with QRS widening.

In addition to these "contour criteria," we adopted the following "amplitude criteria" of aberrancy: Because beat to beat variations in the QRS amplitude of sinus beats were often noted, we first determined the maximal variation in their total QRS amplitude (ΔQRS) in leads showing atrial premature systoles. When the amplitude of a given premature QRS either exceeded that of the largest QRS complex of sinus origin or was smaller than the smallest sinus QRS complex by a

difference greater than ΔQRS, aberrancy in terms of amplitude changes was identified. In the absence of beat to beat QRS variation, a difference of 0.2 mv or greater was arbitrarily chosen to indicate amplitude aberrancy. These two criteria for contour and amplitude aberrancy were not mutually exclusive.

Results

Incidence of aberrant intraventricular conduction: Of the 149 atrial premature systoles studied, 71 were considered to have aberrant intraventricular conduction in terms of the amplitude criteria, whereas 45 showed aberrancy in terms of contour criteria. There were 34 premature beats that satisfied both of these criteria, whereas 67 premature systoles did not show any aberrancy.

The electrocardiogram reproduced in Figure 2 illustrates various degrees of aberrancy. Here, precordial leads V_2, V_4, V_5 and V_6 are shown, of which the latter three were recorded simultaneously. In lead V_2, two atrial premature systoles are noted (beats 4 and 8). Their atrial origin is readily noted from the presence of an early P wave preceding those QRS complexes at a P-R interval of approximately 0.16 second. Their coupling (R_s-R_p) intervals both measure 0.56 second, whereas the Q-aU and Q-eU intervals are 0.50 and 0.60 second, respectively, from beats 2 and 6, which terminate the basic sinus cycle. Thus, these premature QRS complexes occurred 0.06 second after the apex of the U wave and 0.04 second before its end. Their QRS configuration is almost identical to that of the sinus beats, showing an RS pattern. The maximal beat to beat variation in the QRS amplitude of sinus beats in this lead amounts to only 0.5 mm (0.05 mv), whereas these two premature QRS complexes are greater than the largest sinus QRS complex by more than 4 mm (0.4 mv). It is thus evident that the amplitude criteria for aberrancy are satisfied, but there is no aberrancy of contour.

On the other hand, there are four atrial premature systoles in leads V_4 through V_6 (beats 2, 5, 8 and 11) with variable coupling intervals. The 2nd and the 11th (last) beats have the same R_s-R_p interval of 0.48 second (and an aU-R_p interval of −0.02 second) and show a significant change in QRS amplitude (see especially lead V_6). In addition, a closer examination of their contour reveals disappearance of the small embryonic Q wave seen in the sinus beats in these leads. Hence, these premature beats also satisfy the contour criteria for aberrant conduction. Beat 5 occurring with a shorter coupling interval of 0.42 second shows a more obvious contour change, with the development of a deep and wide S wave and QRS prolongation suggesting a conduction delay in the right bundle branch system. In contrast, beat 8 has the longest R_s-R_p interval of

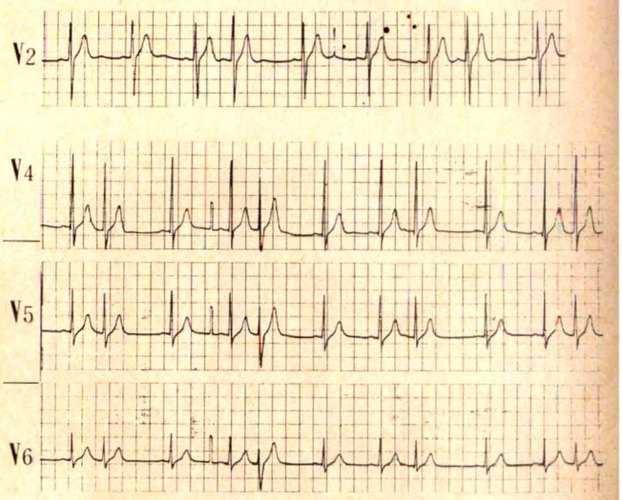

FIGURE 2. Identification of aberrant intraventricular conduction based on contour and amplitude criteria. Detailed discussion in text.

0.54 second but still occurs before the end of the U wave. Although this beat does not show any contour aberrancy, minimal amplitude aberrancy is present.

The validity of the criteria for aberrancy based on alterations in the QRS amplitude, arbitrarily set by us in this study, is supported by the electrocardiogram reproduced in Figure 3, which was obtained from a case not included in our series. In lead V_3 of this record, the presence of right bundle branch block is evident from the QRS duration of 0.13 second and the QRS-T configuration. The Q-aU and Q-eU intervals of the sinus beats measure approximately 0.54 and 0.62 second, respectively. There are two atrial premature systoles in lead V_3 (beats 3 and 8) that have a coupling interval of 0.54 second and occur almost on the apex of the U wave. The QRS complexes of these premature beats retain the right bundle branch block pattern and have a QRS duration of 0.13 second, which is identical to that of the sinus beats. However, a definite increase in their amplitude is readily noted. Thus, alterations in the QRS amplitude appear to signify aberrant intraventricular conduction even in the presence of a bundle branch block. Langendorf[15] reported a similar case although he did not specifically emphasize the change in QRS amplitude (his Fig. 5). In lead III of our Figure 3, two atrial premature systoles (beats 4 and 8) occurred with slightly longer coupling intervals of 0.58 and 0.62 second, respectively, the latter corresponding to the end of the U wave. A slight de-

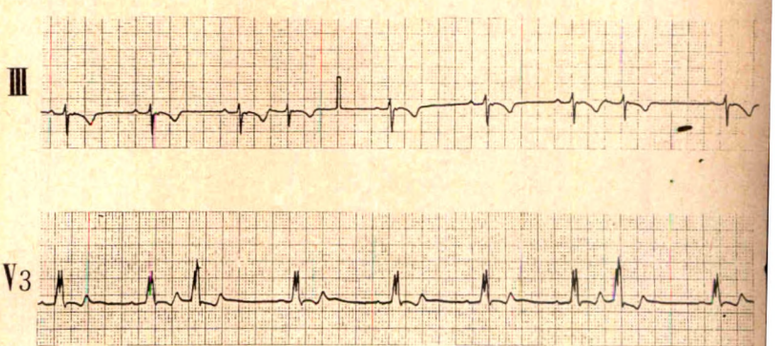

FIGURE 3. Atrial premature systoles revealing amplitude aberrancy in the presence of right bundle branch block.

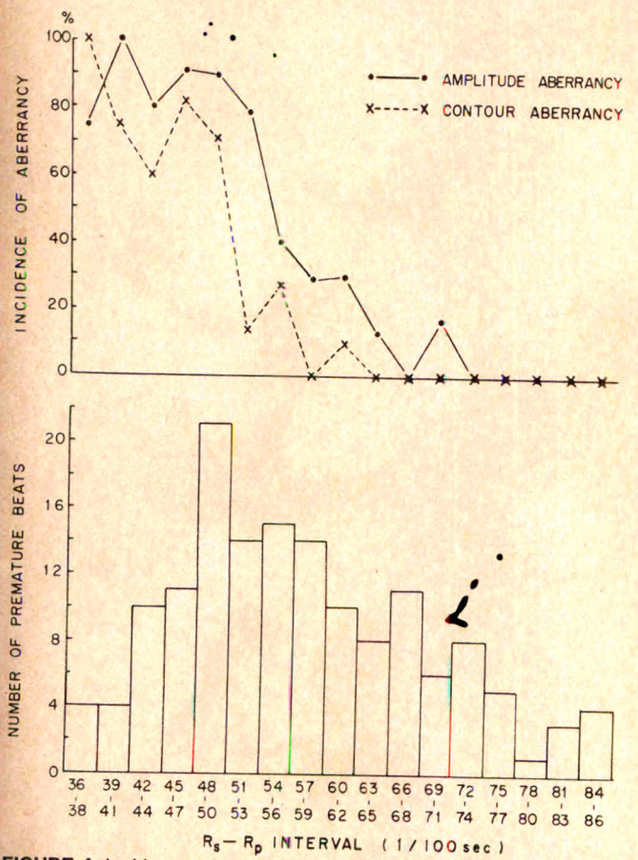

FIGURE 4. Incidence of aberrant conduction as related to the R_s-R_p interval (interval from the beginning of the QRS complex of a sinus beat to that of a coupled atrial premature systole). The histogram **(bottom)** shows the number of premature beats in individual ranges of R_s-R_p intervals; the two curves **at top** show percent incidence of aberrancy based on criteria of amplitude **(solid line)** and contour **(broken line).**

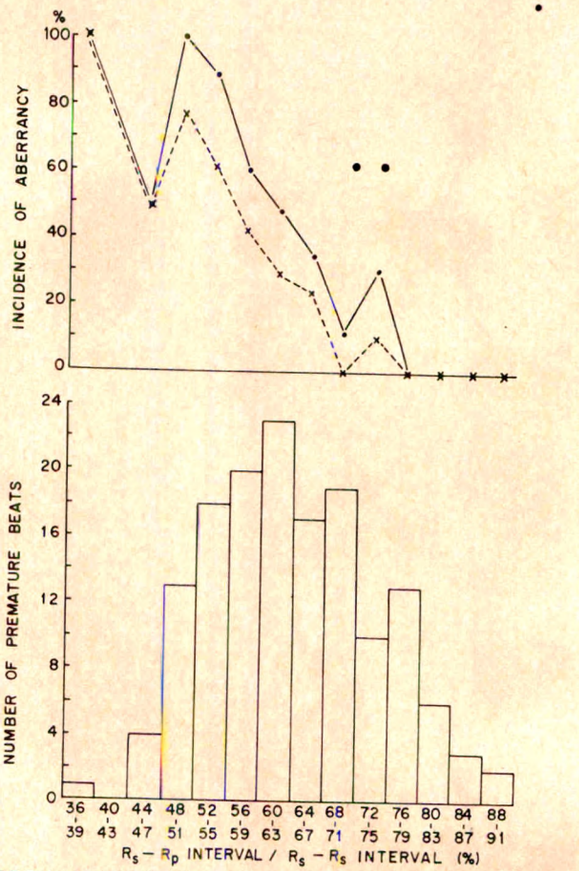

FIGURE 5. Incidence of aberrant QRS complexes as related to the ratio of the R_s-R_p/R_s-R_s intervals. The R_s-R_s interval is the basic sinus cycle length. Histograms and curves similar to those in Figure 4.

crease in their QRS amplitude is noted in beat 4, whereas the amplitude change is hardly significant in beat 8.

Aberrancy correlated with other measurements: After the presence or absence of aberrant intraventricular conduction was determined in individual atrial premature beats in the manner illustrated in Figures 2 and 3, the incidence of aberrancy was plotted against the coupling interval, the ratio between the coupling interval and the basic cycle length, and so forth.

Figure 4 shows such a correlation with the coupling intervals. The histogram at the bottom of this figure shows the number of premature beats in individual ranges of coupling intervals. For instance, the shortest coupling intervals of 0.36 to 0.38 second occurred in four instances, whereas the most common range of R_s-R_p intervals was between 0.48 and 0.50 second (21 instances). In the top diagram, the solid line connecting closed circles indicates percent incidence of aberrancy in terms of amplitude; the broken line with crosses indicates that in terms of contour. Although there is a trend toward an increased incidence of aberrant conduction with the shorter coupling intervals, these two curves are not smooth, and even the shortest observed coupling intervals were not always associated with aberrancy. Thus, the coupling interval as such does not appear to determine the development of aberrant conduction.

In Figure 5 the incidence of aberrancy is plotted against the ratio between the R_s-R_p and R_s-R_s intervals. This ratio is considered an index of sudden shortening of the ventricular cycle and has been commonly believed to play a major role in the genesis of aberrant intraventricular conduction in what is known as the Ashman phenomenon.[3] Although a general trend is again observed toward a greater probability of occurrence of aberrant QRS complexes with a smaller ratio, ratios below 50 percent are often accompanied by no aberrancy in either amplitude or contour. Furthermore, the incidence of contour aberrancy decreases to zero (0 of 19) with a shortening of the R-R cycle to 68 to 71 percent, but a lesser shortening of 72 to 75 percent is again associated with a 10 percent incidence rate (1 of 10). Thus, it appears that there is no critical degree of sudden R-R shortening that invariably causes abnormal intraventricular conduction of supraventricular impulses.

Because an atrial impulse should invade the intraventricular conduction system some time before the inscription of a QRS complex, one might argue that the R_s-R_p/R_s-R_s ratio may not accurately reflect the shortening of cycle length that is truly effective at the His-Purkinje level. Hence, an additional measurement,

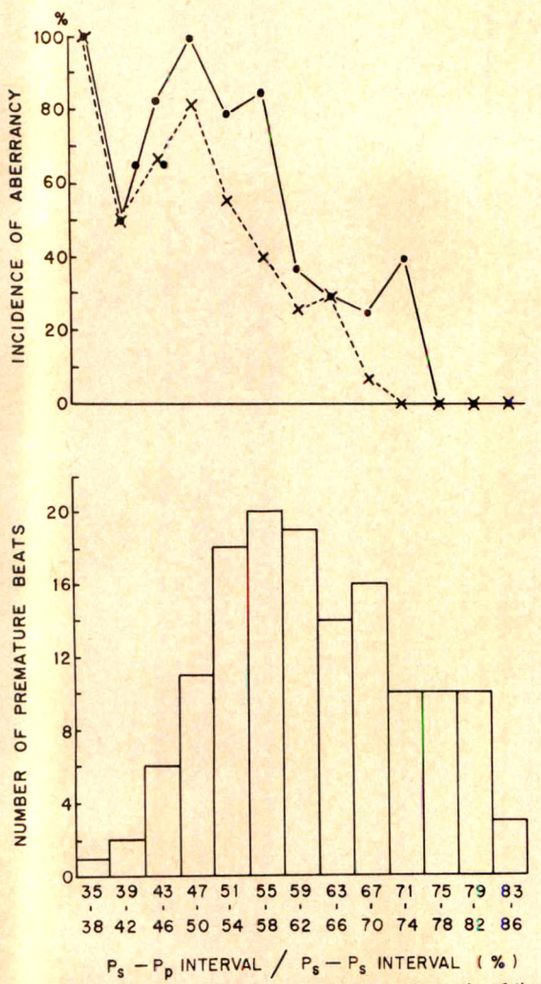

FIGURE 6. Incidence of aberrancy as related to the ratio of the P_s-P_p/P_s-P_s intervals. The P_s-P_p interval is the interval between the P waves of sinus and premature beats; the P_s-P_s interval is the interval between two consecutive sinus P waves.

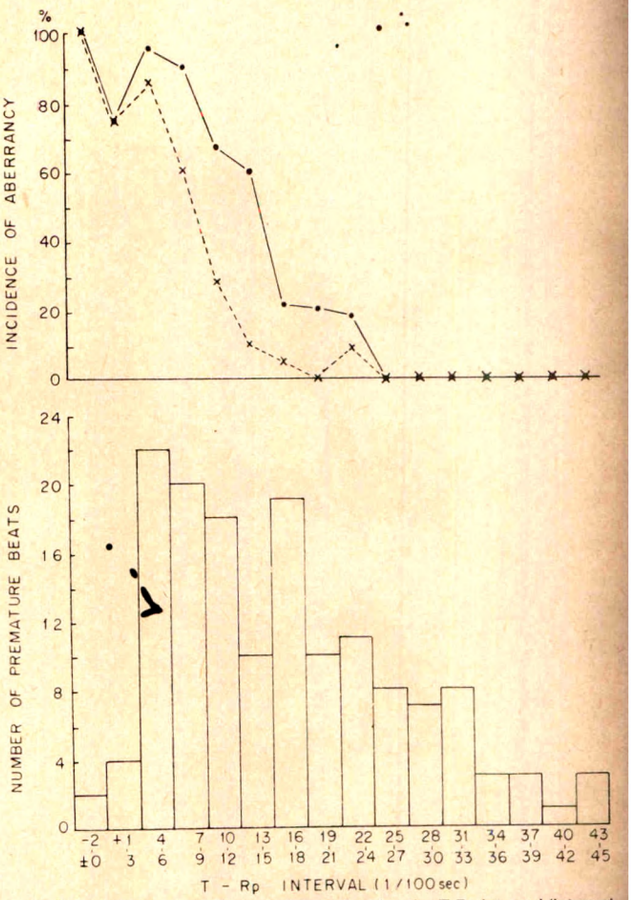

FIGURE 7. Incidence of aberrancy as related to the T-R_p interval (interval between the end of the T wave of a sinus beat and the onset of the QRS complex of an atrial premature systole).

the P_s-P_p interval (the interval between a sinus P wave and a premature ectopic P wave), was also analyzed.

Figure 6 shows the correlation of percent incidence of aberrancy and the ratio of P_s-P_p/P_s-P_s. In this figure the two curves showing aberrancy of amplitude and contour have a pattern similar to those in Figure 5 although the irregularities are somewhat more exaggerated.

Figure 7 shows the relation between the incidence of aberrant conduction and the T-R_p interval. When this interval was less than zero, or when the QRS complex of atrial premature systoles appeared before the end of the preceding T wave (this occurred in only two cases), aberrancy was present in 100 percent (2 of 2). Contrariwise, one of the four atrial premature beats having the next shortest T-R_p intervals of 0.01 to 0.03 second failed to show any signs of aberrancy, thus reducing the incidence rate to 75 percent and making the curves far from smooth.

Figures 8 and 9 illustrate much better correlations between the percent incidence of aberrancy and the timing of atrial premature systoles with reference to the preceding U waves. In Figure 8, the incidence is plotted against the aU-R_p intervals. Here, the relation of amplitude as well as contour aberrancy and the aU-R_p interval show smooth reversed S-shaped curves. Indeed, when this interval was less than −0.01 second, or when premature ventricular activation by an atrial impulse occurred before the apex of the U wave (arrow aU), the resultant QRS complex showed an abnormal amplitude in more than 88 percent and a contour change in more than 76 percent of cases. With a progressive increase in this interval, the probability of having aberrant conduction decreased rapidly. Similarly in Figure 9, the incidence of aberrancy is well correlated with the eU-R_p interval. When the QRS complexes of atrial premature systoles appeared after the end of the U wave (arrow eU), contour aberrancy was never observed and the incidence rate of amplitude aberrancy was less than 10 percent.

These relations between the development of aberrant intraventricular conduction and the timing of atrial premature systoles with reference to the U wave of the preceding sinus beat are further illustrated in Figure 10. In this case with frequent atrial premature beats, the coupling intervals showed wide fluctuations suggesting possible atrial parasystole. During the initial control period, the sinus rate was 64/min, and the Q-aU and Q-eU intervals measured 0.51 and 0.62 second, respectively, as indicated by the downward arrows aU and eU. Six of seven premature beats appeared before the end of the U wave, all of which were associated with some degrees

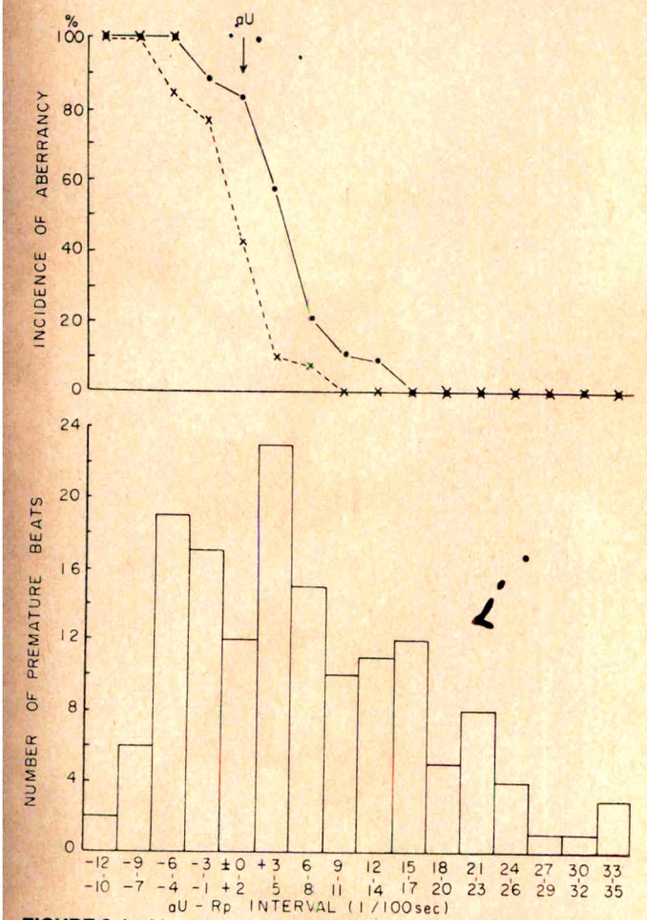

FIGURE 8. Incidence of aberrancy as related to the aU-R_p interval (interval from the apex of the U wave [aU] of a sinus beat to the beginning of the QRS complex of an atrial premature systole).

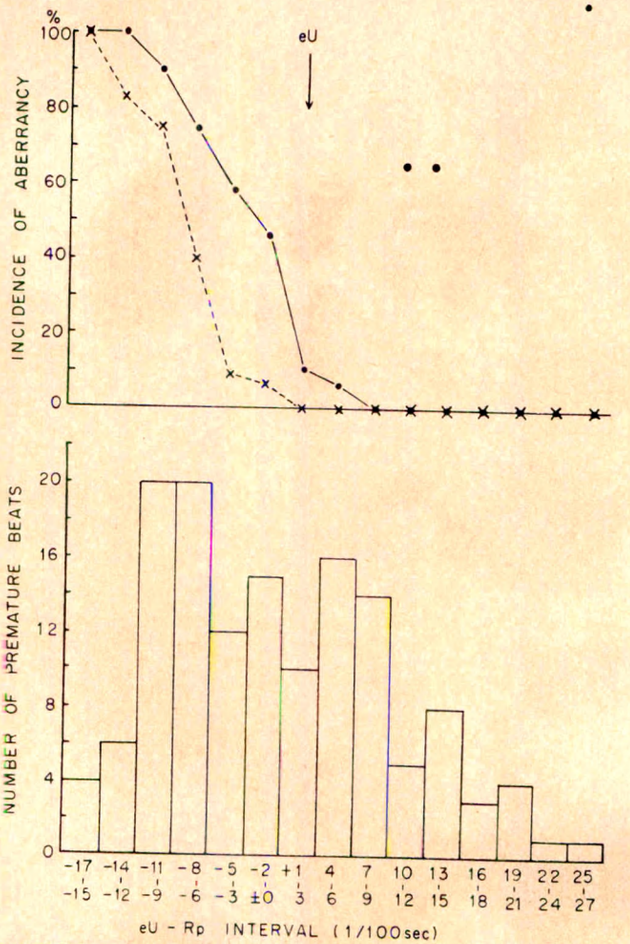

FIGURE 9. Incidence of aberrancy as related to the eU-R_p interval (interval from the end of the U wave [eU] of a sinus beat to the beginning of the QRS complex of an atrial premature beat).

of aberrant conduction (solid squares). In contrast, one premature systole occurring at a coupling interval of 0.64 second (0.02 second after the end of the U wave), did not show aberrancy (open square). When this patient performed exercises, the sinus rate increased to 82/min, with a concomitant shortening of the Q-aU and Q-eU intervals (upward arrows aU and eU). Fifteen atrial premature systoles were observed after exercise, of which 10 showed aberrant QRS complexes, whereas the remaining 5 did not. This figure again demonstrates that the end of the U wave determines the appearance or nonappearance of aberrant conduction.

Atrial premature beats showing bundle branch block: In this study, aberrant conduction showing a typical right or left bundle branch block configuration with QRS widening of 0.12 second or greater was observed in 14 instances. These atrial premature systoles were studied with regard to the aU-R_p interval as well as the ratio between the R_s-R_p and R_s-R_s intervals, and the results are shown in Figure 11.

Several comments are in order on Figure 11: (1) A right or left bundle branch block pattern of aberrancy was never observed with a positive aU-R_p interval. In other words, the occurrence of premature QRS complexes before the apex of the U wave appears to be a prerequisite to the production of a typical bundle branch block configuration. The reverse is not necessarily true because many atrial premature beats having a negative aU-R_p interval showed lesser degrees of aberrancy of contour (or amplitude). (2) On the other hand, these bundle branch block patterns of aberrant conduction were observed when the ratio between the coupling interval and the basic sinus cycle length was less than 57 percent although, again, many more atrial premature systoles with such R_s-R_p/R_s-R_s ratios showed either lesser degrees of aberrancy or no aberrancy at all. (3) There is a general trend that the right bundle branch block type of aberrancy occurs with relatively less degrees of prematurity, whereas the left bundle branch block configuration is produced with greater prematurity or only when an atrial premature systole precedes the apex of the U wave by intervals of 0.05 second or longer. Contrariwise, the values of R_s-R_p/R_s-R_s ratio do not appear to determine the patterns of bundle branch block. (4) One exception to the tendency of a right bundle branch block configuration to occur with lesser degrees of prematurity was noted when a premature QRS complex at an aU-R_p interval of −0.12 second had a right bundle branch block configuration (cross with arrow). However, this was a special case of atrial bigeminy in which the first atrial premature beat showed a left bundle branch block pattern at an aU-R_p interval of −0.09 second (closed circle with arrow), whereas the second premature systole was associated with the right bundle branch block. Such alternating patterns of aberrant ventricular conduction in the presence of atrial bigeminy were reported

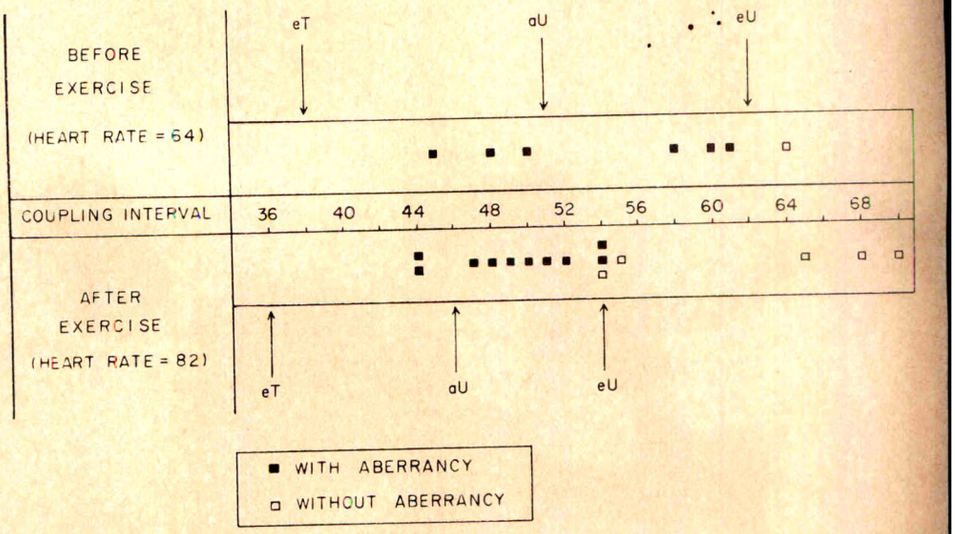

FIGURE 10. Interrelations between the time of appearance of atrial premature systoles and aberrant conduction before and after exercise (heart rate 64 and 82 beats/min, respectively) in a case of possible atrial parasystole. Coupling intervals in 1/100 sec. eT, aU and eU represent the end of the T wave, the apex of the U wave and the end of the U wave, respectively, as illustrated in Figure 1. See text for discussion.

earlier by Katz and Pick[16] and later experimentally produced in man by Cohen et al.[17] The latter discussed possible electrophysiologic mechanisms of this peculiar phenomenon.

Discussion

Disturbances of impulse transmission in myocardial tissues result from many factors that have been extensively reviewed by Watanabe and Dreifus,[18] and Singer and Ten Eick[8] have discussed the electrophysiologic mechanisms of aberrant conduction in detail. Aberrant intraventricular conduction is seen not only with a shortening of the ventricular cycle length but also with its prolongation.[4–6] The latter is probably caused by diastolic depolarization of certain Purkinje fibers, which results in a loss of membrane potential in late electrical diastole and decreased conductivity of propagated responses arising from such reduced potential levels.[19] Some investigators[20] have termed this mechanism phase 4 block. Contrariwise, aberrant conduction associated with shortened cycle lengths is caused by activation of Purkinje fibers before the completion of repolarization, which is often called phase 3 block.[20] Aberrancy of atrial premature systoles as observed in our cases probably results from this latter mechanism.

Theoretically, if conduction velocity in all the Purkinje fibers is decreased to the same extent, the resultant QRS complex may simply be widened without any alterations in contour although the QRS amplitude may well be modified. However, the time course of repolarization as well as recovery of excitability usually shows fluctuations between different fascicles or even from one Purkinje fiber to another in a given fascicle. Thus, premature stimulation of these fibers causes asynchronous spread of ventricular excitation[21] and, hence, aberrant conduction.

Aberrant conduction and transnodal (A-V) conduction: Whether the ventricular Purkinje fibers are activated during their phase 3 repolarization obviously depends on the degree of prematurity of a supraventricular impulse or the interval between the sinus and premature P waves (P_s-P_p interval). However, an extremely premature atrial impulse tends to sustain a greater conduction delay within the A-V node and may sometimes arrive in the fascicles of the intraventricular conducting system even later than certain less premature impulses that traverse the A-V node at greater velocities (so-called gap phenomenon).[22,23] Thus, several authors[24,25] have pointed out the importance of transnodal conduction time in the development of aberrant conduction. Indeed, studies using His bundle electrography have shown that the H_1-H_2 interval (or the interval between the His deflections caused by a sinus and a premature beat) plays a major role in aberrancy of atrial premature beats.[25] Although such measurements were not available in our electrocardiographic study, the effects of intranodal conduction delay were at least partially corrected by using the interval between the QRS complex of a sinus beat and that of the atrial premature systole (R_s-R_p interval) instead of the P_s-P_p interval (Fig. 4).

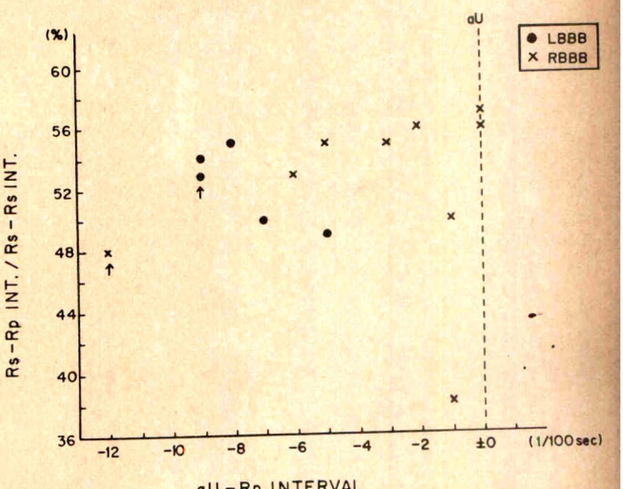

FIGURE 11. Correlation of a typical left (LBBB) or right (RBBB) bundle branch block pattern of aberrancy with the aU-R_p interval as well as the ratio of the R_s-R_p/R_s-R_s intervals. Detailed discussion in text.

Aberrant conduction, cycle length and coupling interval (Ashman phenomenon): On the other hand, the duration of both the transmembrane action potential and the effective refractory period shows a positive correlation with the cycle length of excitation.[26] Consequently, a longer preceding cycle is associated with a slower repolarization of Purkinje fibers, thus facilitating encroachment of their phase 3 by a premature impulse. It is then readily understood that the R_s-R_p interval (coupling interval) as such would not show a good correlation with the incidence of aberrant QRS complexes (Fig. 4), and the combination of a slower basic rhythm and a shorter coupling interval (or a greater degree of cycle length shortening) would definitely favor the development of aberrant conduction. This relation was first pointed out by Gouaux and Ashman[3] and is commonly referred to as the Ashman phenomenon. Many investigators have repeatedly stressed the importance of longer preceding cycles on the basis of both clinical and experimental observations.[7,8,14,15,24,25]

In our study the curves correlating the incidence of aberrancy and the ratio of the R_s-R_p/R_s-R_s intervals (this is a measure of the degree of sudden cycle length shortening) were not as smooth as might be expected from the preceding arguments for the Ashman phenomenon (Fig. 5). Such findings probably reflect variations in the time course of Purkinje repolarization from one case to another or even from one moment to the next in a same heart. Hence, a particular combination of R_s-R_p and R_s-R_s intervals (or even a particular H_1-H_2 interval) does not necessarily result in the encroachment of an identical point of phase 3 repolarization by the premature atrial impulses in two different instances, and the relation expressed by the Ashman phenomenon applies only in general terms. The lack of good correlation between the P_s-P_p/P_s-P_s ratio and the incidence of aberrancy (Fig. 6) obviously resulted from an additional involvement of intra-A–V nodal conduction time as discussed previously.[24,25]

The T wave as an index of phase 3 repolarization: It may thus be construed that if there is any good index for the phase 3 repolarization of the intraventricular conducting fibers, this index should show a much better correlation with the incidence of aberrant conduction of atrial premature systoles. Because the Purkinje fibers show a longer duration of action potential than the ventricular muscle fibers,[27] an indirect estimation of the time of Purkinje repolarization may be made from the T wave. However, the difference between action potential durations of Purkinje and ventricular muscle fibers is affected by many factors including heart rate,[13] and no fixed time values can be assigned between the T wave and phase 3 of the Purkinje system. This explains the still not smooth curves correlating the T-R_p interval (the interval between the end of the T wave and the premature QRS complex) and the incidence of aberrancy (Fig. 7) although the correlation appeared to be a little better than that obtained with the other three variables.

Aberrancy and the U wave (an index of phase 3 repolarization of the Purkinje system): When the distance of the QRS complex of an atrial premature systole from either the apex (aU) or the end (eU) of the U wave of the preceding sinus beat was correlated with aberrant conduction, the curves were quite smooth (Fig. 8 and 9). This finding suggests that the relative timing of the U wave and premature QRS complex plays a decisive role in producing aberrant intraventricular conduction, a hypothesis further substantiated in Figure 10. From these considerations, our premise that the U wave of the electrocardiogram probably represents phase 3 repolarization of the Purkinje system (or the Purkinje T wave) appears to be supported.[11–13]

It is well known that aberrant conduction of supraventricular premature systoles most commonly shows a right bundle branch block configuration.[3,6,8,28] On the basis of experimental studies in canine Purkinje preparations,[29] this finding has been attributed to the presence of longer action potential durations in the right than in the left bundle branch. If this holds true also in man, it may be suggested that repolarization of the left bundle branch fibers contributes to the initial portion of the U wave while repolarization of the right bundle branch system is responsible for the terminal portion of this wave form. The appearance of aberrancy of the left bundle branch block type only when premature QRS complexes occur 0.05 second or more earlier than the apex of the U wave, and the common production of right bundle branch block pattern when they occur toward the apex of the U wave (Fig. 11) may be in keeping with the above hypothesis. One possible explanation for the appearance of left bundle branch block in the presence of longer action potential durations in the right bundle is that conduction is only delayed in the latter while it is blocked in the left bundle entirely with such short coupling intervals; however no insight into this question is gained from our study.

So-called incomplete right bundle branch block patterns were often noted in atrial premature systoles occurring after the apex (but before the end) of the U wave (not shown). Moore et al.[30] indicated that a right bundle branch block configuration resulted from a block in the proximal portion of the right bundle and an incomplete right bundle branch block from a distal block. Cohen et al.[24] thought that a right bundle branch block pattern with the initial QRS vector identical to that of the sinus beats was due to distal Purkinje block, whereas that with a different initial vector was caused by proximal block. In vitro and in vivo experiments by Toyama[9] localized the site of conduction delay and block of premature stimuli slightly more proximal to the so-called distal gate of the right bundle. Obviously, no information on the level of conduction block is available in studies using clinical electrocardiograms alone. However, Moe et al.[7] earlier concluded that aberrant conduction was never caused by the refractoriness in ventricular muscle itself.

Other causes of aberrancy of premature beats: Several investigators[6,8] have mentioned possible causes of aberrant conduction of supraventricular premature beats other than incomplete repolarization of the Purkinje fibers. For instance, the use of certain anomalous A-V pathways by a supraventricular premature impulse

could cause an aberrant QRS complex. Although no cases with apparent preexcitation were included in our series, the presence of so-called concealed bypass tracts cannot definitely be ruled out. This or certain other mechanisms of aberrancy may have been responsible for some of the instances in which QRS complexes occurring beyond the end of the U wave showed minor degrees of aberrant conduction (Fig. 9).

Other views on genesis of the U wave: Finally, comments are in order on another prevailing theory on the genesis of the U wave. In an early panel discussion,[31] several investigators suggested that negative afterpotentials in the ventricular myocardium caused this electrocardiographic wave form. A more recent review by Lepeschkin[10] again considered this theory the most plausible and did not favor the theory of Purkinje repolarization. If one subscribes to the afterpotential theory, one might hypothetically propose that the arrival of a supraventricular impulse in the working ventricular muscle fibers at the time of a negative afterpotential may alter the upstroke velocity of their action potential and cause an abnormal spread of intramural excitation even though the bulk of evidence discussed seems to support the so-called phase 3 block in the Purkinje fibers as the cause of aberrant conduction. However, we believe that with this afterpotential mechanism one would expect the greatest degrees of aberrancy to develop when a premature QRS complex occurs on or around the apex of the U wave where the cell membrane is said to be unstable and the excitability is enhanced.[10,32] Contrariwise, aberrancy of premature QRS complexes becomes further exaggerated with their progressively early appearance with reference to the apex of the U wave (Fig. 2 and 11).

In conclusion, the Purkinje repolarization theory appears to offer more plausible explanations for at least several clinical electrocardiographic findings related to the U wave[11,12] although the validity of this concept still rests on more direct experimental studies to be carried out in the future.

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Valve Origin of the Aortic Incisura

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The occurrence and magnitude of the incisura of the central aortic pressure were shown in 66 patients to depend on the functional state of the aortic valve. In normal subjects and children with congenital aortic stenosis (with thin flexible leaflets), the incisura ranged between 6 and 14 mm Hg. With aortic regurgitation, the incisura diminished as the severity of regurgitation increased. With calcific aortic stenosis, the incisura was smaller or absent. These observations imply a valve mechanism productive of the incisura. In vitro studies of human aortic valves confirmed these observations. Additional in vitro studies with high speed cinematography (2,000 frames/sec) of a stented normal porcine valve also showed that early diastolic stretch and recoil of the leaflets occurs. These results indicate that in the presence of a normal or diseased aortic valve the aortic incisura is produced primarily by valve distension or recoil, respectively. Distension and rebound of the aortic walls do not appear to contribute significantly in the presence of a normal or a diseased valve. Because acquired aortic valve disease affects the magnitude of the central aortic incisura, inspection of the incisura may be of ancillary value in evaluating the pathologic state of the aortic valve.

The incisura of the central aortic pressure, frequently termed the dicrotic notch, has been observed since intraarterial catheterization was first introduced. However, its mechanism of production has not been fully explored. Pressure within the aorta has been thought to reflect the volume of blood contained within the vessels and the distensibility characteristics of the aortic wall.[1] This would imply that the incisura results from transient distension of the aorta. Others[2] considered the incisura the result of closure of the aortic valve, but they did not describe the method by which closure produces the incisura. The aortic incisura has been postulated to result from the rebound of the aortic blood column and walls that occurs after aortic valve closure.[3] Burton[4] described the aortic incisura or dicrotic notch as an interruption of the decrease of aortic pressure that occurs after abrupt closure of the aortic valve. He suggested that the elastic recoil of the aorta and of the valve itself creates the increase in pressure productive of the dicrotic wave. In view of the limited information upon which these speculations were made concerning the origin of the aortic incisura, we attempted to provide a more detailed view of the mechanism producing this phenomenon. Recognition of the exact cause of the aortic incisura would explain the variability of the incisura in various diseases of the aortic valve.

Methods

Clinical studies: Central aortic pressure was measured in 66 patients during diagnostic cardiac catheterization. Twenty-six patients had a normally functioning aortic valve as judged from the absence of a pressure gradient across the aortic valve, the absence of murmurs and normal cineaortograms in 10 of 26 patients with aortographic studies. Sixteen patients had pure aortic insufficiency of various degrees of severity. Aortic insufficiency in these patients was quan-

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titated from cineaortograms on the basis of a 1+ to 4+ scale.[5] Twenty patients had mild to severe calcific aortic stenosis combined with mild to moderate aortic regurgitation. Three patients had congenital aortic stenosis, as judged from a history of a murmur since birth, their age (3, 10 and 20 years, respectively) and a pressure gradient across the aortic valve (44 to 70 mm Hg). None of these three patients had aortographic evidence of aortic insufficiency. One patient with calcific aortic stenosis was studied before and after the insertion of a porcine heterograft aortic prosthetic valve.

Aortic pressures were obtained using a Millar catheter-tip micromanometer in 24 patients and a fluid-filled catheter in conjunction with a Statham P23db pressure transducer in 42 patients. The tip of the catheter was routinely placed in the ascending aorta in proximity to the aortic valve. All recordings were made using an Electronics for Medicine photographic recorder at paper speeds of 25 to 200 mm/sec.

To determine the variability of the aortic incisura associated with various abnormalities of the aortic valve, the incisura was quantitated in two ways: (1) the magnitude of the aortic incisura was measured in millimeters of mercury from the bottom of the incisura to the top of the dicrotic wave; and (2) the ratio of the magnitude of the aortic incisura to the magnitude of the aortic pulse pressure (millimeters of mercury) was calculated.

In vitro studies: These were performed utilizing a Plexiglas® model of the root of the aorta and left ventricular chamber in which various types of valves were inserted. The dimensions of the simulated root of the aorta were based on measurements obtained from aortograms of normal subjects, and these dimensions were within the range described by others.[6] The simulated arterial circulatory system was previously described in detail.[7,8] Essentially, the system consisted of a reservoir, a hydraulic pump, a compression chamber, a laminar resistor and a variable clamp. The parts were interconnected through a series of various types of rigid and corrugated rubber tubing. A Statham P23db pressure transducer was connected directly to the model of the aortic root through a precision-drilled orifice in the Plexiglas. Systolic pressure was adjusted by varying the fluid level in the compression chamber, and diastolic pressure was adjusted with the variable clamp distal to the compression chamber. The test fluid consisted of a mixture of water and glycerin with a viscosity of 0.05 poise.

Various configurations of human valves were studied in vitro: These included a normal human valve, a thickened and deformed stenotic human valve, a stenotic valve with normally flexible and distensible leaflets and an insufficient human valve. The normal human valve was obtained at autopsy and mounted on stents. The cross-sectional area of its orifice was 5 cm^2. A second human valve was mounted in a similar fashion and was made to simulate a severely thickened and deformed valve. The leaflets were sealed and thickened with silicone adhesive, which resulted in a thickness of 0.1 to 0.3 cm. The effective orifice area was reduced to 0.7 cm^2. A valve that simulated a congenitally stenosed aortic valve with normally flexible leaflets was made from a normal human valve mounted on stents; the leaflets were sewn together with 5-0 sutures, leaving a central orifice of 0.8 cm^2. The leaflets closed completely during diastole, permitting no regurgitation. An insufficient semilunar valve was created from a stented normal human valve by suturing open one of the leaflets.

Valves were tested in the simulated arterial system at a constant pump rate of 68 strokes/min, a stroke volume of 80 ml/stroke and an aortic pressure of 120/80 mm Hg. (However, the pressure with the insufficient valve was 125/65 mm Hg.) The systolic ejection period was maintained at 0.29 second

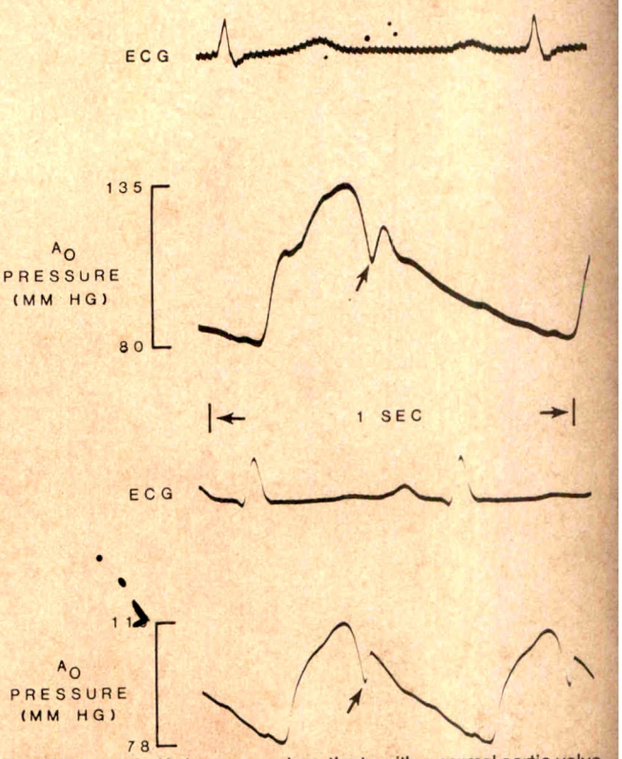

FIGURE 1. Aortic (A_O) pressures in patients with a normal aortic valve, showing prominent deeply inscribed incisuras **(arrows). Top,** pressure measured with a fluid-filled catheter. **Bottom,** pressure measured with a catheter-tip micromanometer. ECG = electrocardiogram.

with the normal valve and the insufficient valve. It was increased to 0.40 to 0.41 second with the stenosed valves to simulate the prolonged ejection that occurs in aortic stenosis.

Cinematography of the motion of the cusps of a stented normal porcine valve in early diastole was performed with a Hycam High Speed Camera (Red Lake Laboratories, Inc., Sunnyvale, California) at 2,000 frames/sec in the in vitro circulatory system that was adapted for such cine pictures. The simulated aortic pressure for these cine films was set at 160/90 mm Hg, the pump rate at 65 strokes/min and the stroke volume at 70 ml/stroke. Cine films of the motion of the valve cusps in early diastole were taken at 90° to the direction of flow.

Results

Clinical studies: *Patients with a normal aortic valve* had a prominent clearly defined sharp incisura (Fig. 1). The amplitude of the incisura varied among patients but was present and well defined in all normal subjects. There was no statistically significant difference between the magnitude of the incisura in the 13 normal subjects whose aortic pressure was measured with a catheter-tip micromanometer and the 13 subjects whose pressure was measured with a fluid-filled catheter. In patients with a normal aortic valve, the incisura ranged from 6 to 14 mm Hg (mean 9 mm Hg). The ratio of the magnitude of the incisura to the magnitude of the pulse pressure ranged from 0.13 to 0.39 mm Hg (mean 0.22 mm Hg).

The three patients with congenital aortic stenosis had a prominent aortic incisura. Both the magnitude of the incisura and the ratio of the incisura to the pulse pressure were within the range observed in patients with a normal aortic valve (Fig. 2).

Studies in patients with pure aortic insufficiency showed an aortic incisura of various degrees of magnitude (Fig. 3). The magnitude decreased (although not necessarily linearly) with an increasing severity of aortic regurgitation (Fig. 3 and 4). The incisura was completely absent in all patients with massive aortic insufficiency (Fig. 3 and 4). Similarly, the ratio of the magnitude of the incisura to the pulse pressure diminished with increasing severity of aortic regurgitation (Fig. 4).

Patients with calcific aortic stenosis and regurgitation also had an incisura of lower amplitude than that of normal subjects. Both the amplitude and the ratio of the incisura to pulse pressure diminished with increasing pressure gradients across the aortic valve (Fig. 2 and 5).

Aortic pressure measurements before valve replacement in a patient with a severely stenotic and calcified aortic valve showed no aortic incisura. After the valve was replaced with a porcine heterograft, the aortic incisura was present and well defined (Fig. 6).

In vitro studies: These confirmed the observations made in patients. A prominent aortic incisura was shown with both the stented normal human valve and the simulated congenitally stenosed human valve. Pressures obtained with the thickened and deformed stenotic valve, which simulated a heavily calcified aortic valve, showed the virtual absence of an aortic incisura.

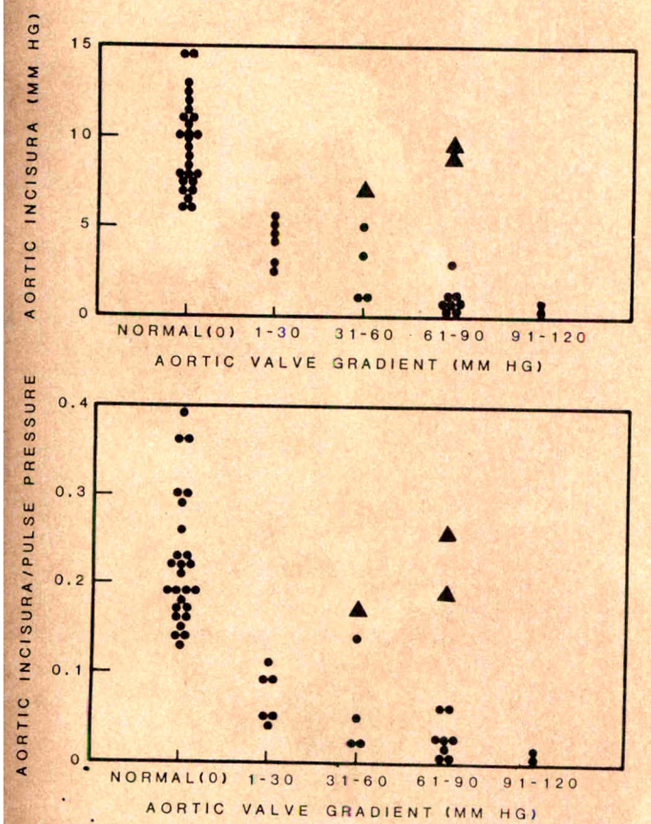

FIGURE 2. Magnitude of aortic incisura (mm Hg) **(top)** and ratio of aortic incisura to pulse pressure **(bottom)** shown in relation to the peak pressure gradient measured across the aortic valve. Both the magnitude of the incisura and the ratio of the incisura to the pulse pressure diminished with increasing pressure gradients in patients with calcific aortic stenosis. However, in young persons with congenital aortic stenosis **(triangles)**, incisuras were of the same magnitude as in normal subjects.

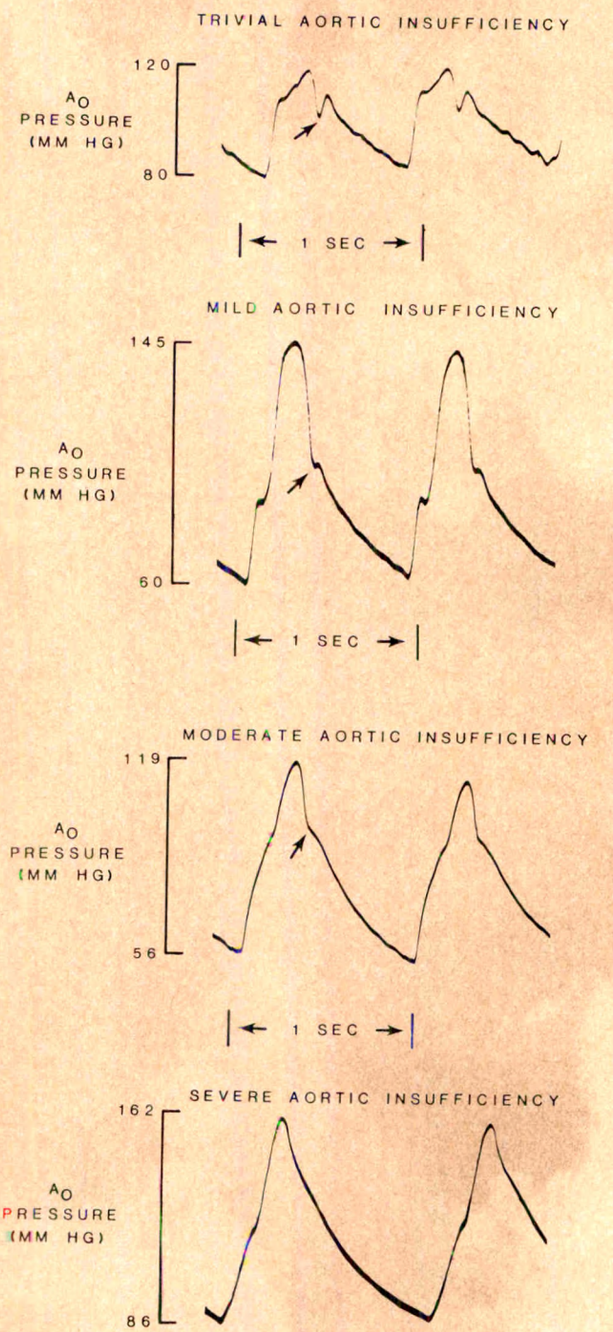

FIGURE 3. Central aortic (A_O) pressures measured in patients with various degrees of aortic insufficiency. No patient had a measurable pressure gradient across the aortic valve. The magnitude of the aortic incisura diminished with an increasing severity of insufficiency.

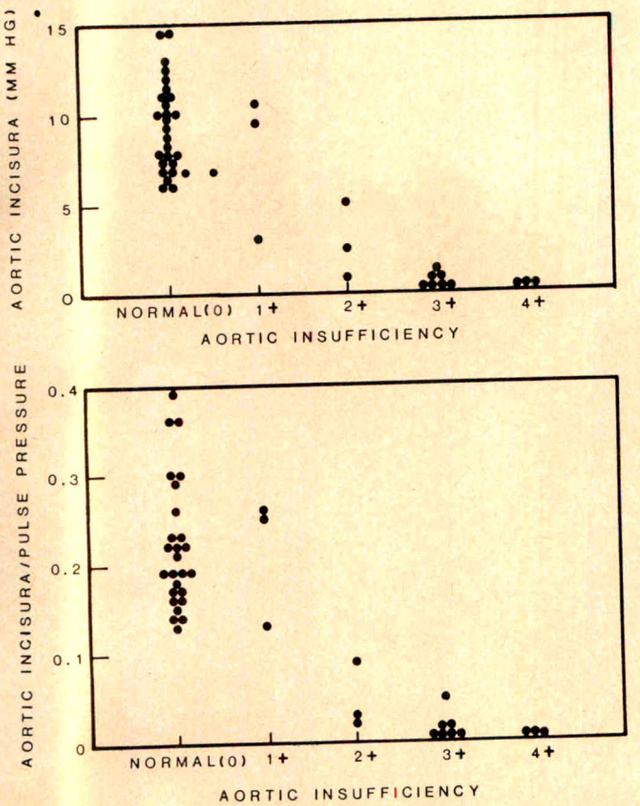

FIGURE 4. Magnitude of aortic incisura **(top)** and ratio of aortic incisura to pulse pressure **(bottom)** in normal subjects and patients with aortic insufficiency of varying degrees of severity as judged by the cineaortogram. Trivial, mild, moderate and severe aortic insufficiency are indicated as 1+ to 4+, respectively.

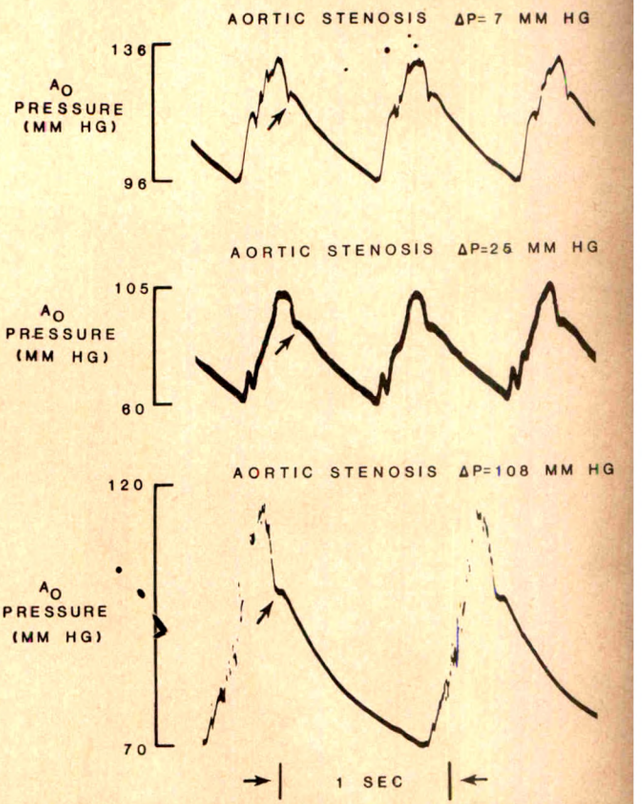

FIGURE 5. Central aortic (A_O) pressure in patients with various degrees of calcific aortic stenosis. Peak pressure gradient (ΔP) measured across the valve is shown. The incisura is indicated by **arrows.** The magnitude of the incisura was small in the patients with the higher gradients.

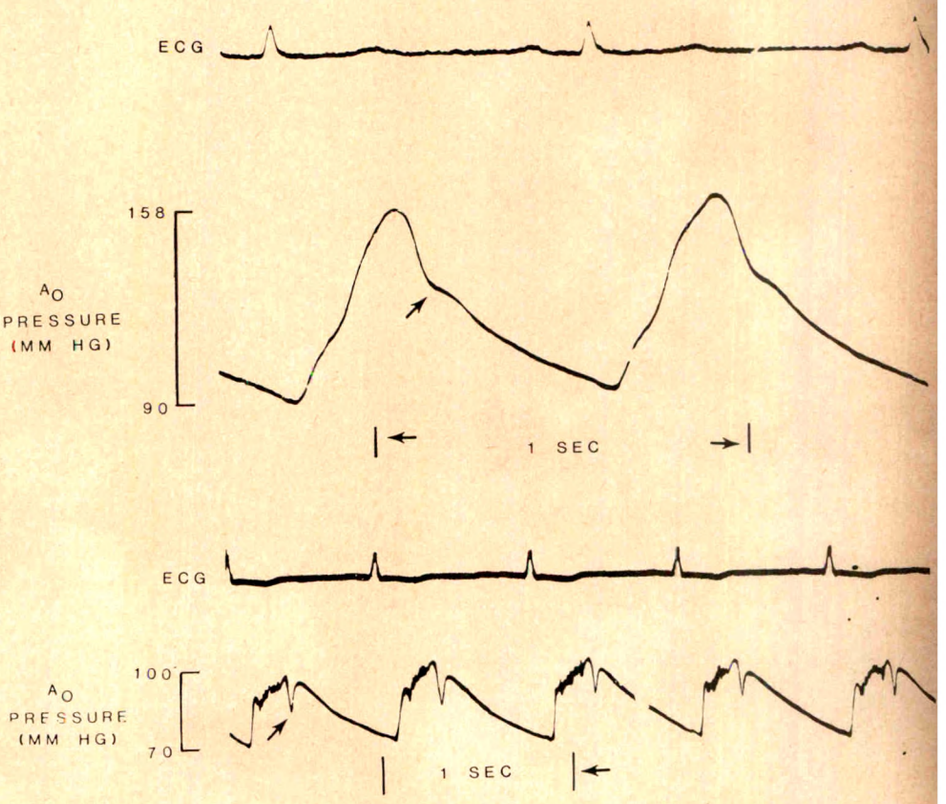

FIGURE 6. Central aortic (A_O) pressure of a patient with calcific aortic stenosis and regurgitation. **Top**, preoperatively, showing an aortic incisura of negligible size **(arrow). Bottom,** after replacement of the aortic valve with a porcine heterograft valve. A prominent deeply inscribed aortic incisura is now shown. ECG = electrocardiogram.

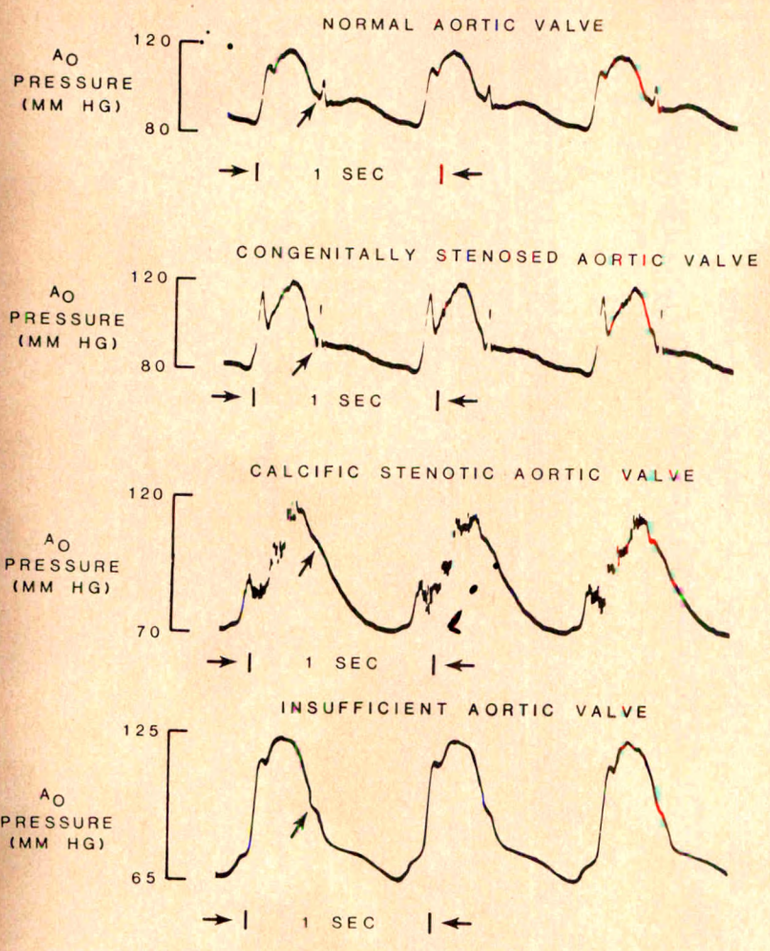

FIGURE 7. Simulated aortic (A_O) pressures, measured in vitro with a stented normal human aortic valve **(top)**, a simulated congenitally stenosed valve, a simulated human calcific stenotic valve and a simulated human regurgitant valve **(bottom)**. The incisura in each case is shown by **arrows.**

The incisura was also of negligible size in the presence of an insufficient valve (Fig. 7).

Cinematography of the aortic leaflets of a porcine valve during diastole showed distension and recoil of the leaflets after closure of the valve (Fig. 8). The center of the cusps bulged into the simulated left ventricle and recoiled toward the simulated aorta after maximal distension.

Discussion

The aortic incisura in patients with a normal or diseased aortic valve: Our results show that under normal physiologic circumstances, and even in the presence of altered physiology induced by a diseased valve, the aortic incisura appears to be produced primarily by the aortic valve. This is apparent from the varying magnitude of the incisura in association with various configurations of the valve. A prominent incisura invariably occurred with a normal aortic valve and a congenitally stenotic valve, reflecting the thin, flexible and distensible leaflets of both normal valves and congenitally stenotic valves. A pressure differential between the aorta and left ventricle at the onset of diastole could readily stretch such valves. A poorly defined and frequently negligible incisura of low amplitude occurred with calcified stenotic valves. A diminished dicrotic notch also has been observed by others[2] in carotid pulse tracings of patients with valve stenosis. This reflects the thickened, noncompliant and nondistensible nature of these valves, which are unable to stretch and respond to the rapidly increasing pressure difference across the valve during early diastole. The magnitude of the incisura diminished with higher systolic gradients across the aortic valve in patients with calcific aortic stenosis. This demonstrated further the dependence of the incisura upon valve distensibility because increased thickening and rigidity of the valve are usually associated with more severe stenosis.

The incisura was also of low amplitude in patients with pure aortic regurgitation, and its magnitude was greatly diminished with more severe regurgitation. An indistinct dicrotic notch in carotid pulse tracings of patients with severe aortic insufficiency has also been observed by others.[2] The reason for the diminished amplitude of the incisura in the presence of aortic regurgitation differs from that of calcific aortic stenosis. In aortic regurgitation, the leaflets have a diminished capacity to become tense after closure. Because such tension is an essential requirement for stretching of the valve, the valve cannot distend into the left ventricle.

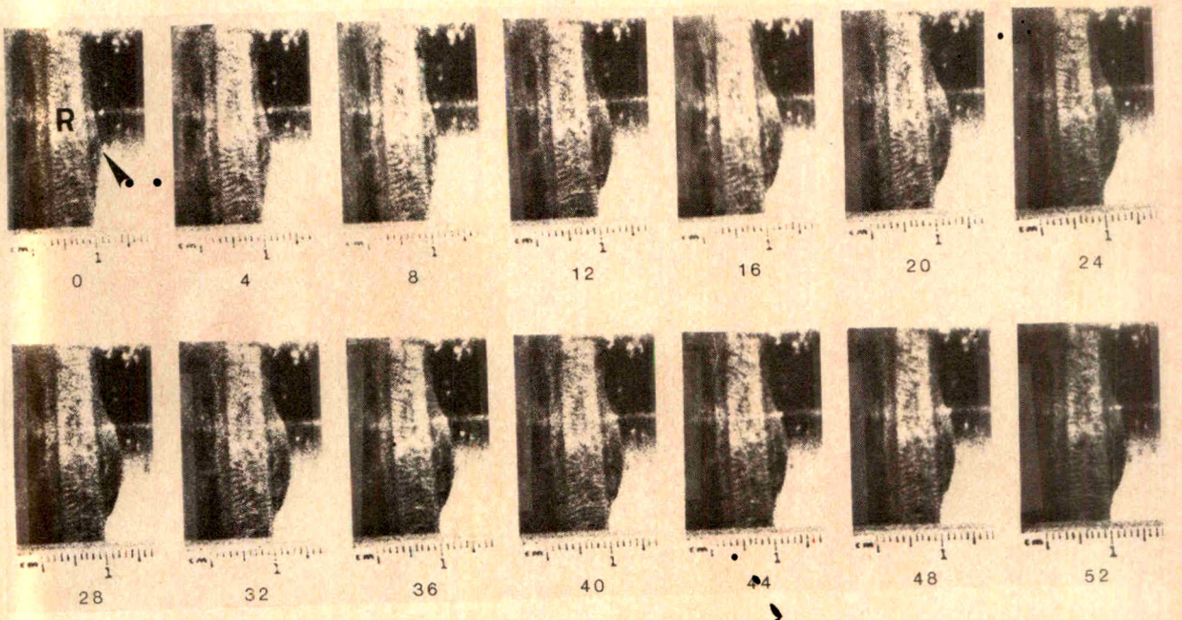

FIGURE 8. Cine films showing stretch and recoil of the closed cusps of a stented normal porcine valve in vitro. The motion pictures of the valve were taken at 90° to the direction of flow. The simulated ventricle is to the **right;** the aorta to the **left.** The sewing ring (R) of the valve is shown with the base of the cusp **(arrow)** protruding toward the ventricle. Diastolic pressure was 90 mm Hg. Every fourth frame was selected for illustration, and the frame numbers are shown. The interval between illustrated frames is 2.0 msec. At the moment of complete closure (frame 0) the base of the cusps extended 0.1 cm from the edge of the sewing ring. This corresponded to the 1.1 cm mark on the accompanying scale. Prominent stretch of the cusps is apparent on frame 24 (1.3 cm mark). Recoil is apparent on frame 44 (1.2 cm mark).

Observations related to the effects of the aortic valve upon the incisura were strengthened by the following demonstration. An incisura of negligible size was shown in a patient who had calcific aortic stenosis before surgery. The incisura was greatly increased after replacement of the valve with a heterograft porcine valve. The difference appears to be attributed to the valve.

Mechanisms contributing to the aortic incisura: The observations made in patients were confirmed in vitro under circumstances that permitted all variables to be uniform and controlled. Only the configuration of the valve was changed in these in vitro studies. With stenotic valves, the duration of systole was correspondingly changed to simulate flow in patients more closely. The incisura in vitro showed characteristics similar to those of the incisura in patients.

Stretch and recoil of the normally distensible valve leaflets thus appear to be the primary cause of the aortic incisura under normal and pathologic circumstances. Distension of the semilunar cusps into the left ventricle occurs because of a differential pressure between the ventricle and the aorta just after valve closure. Such ballooning causes a transient increase of the volume of the root of the aorta. A small amount of blood drains from the aorta into the distended cusps and causes a rapid reduction of the aortic pressure, the end point of which is the apex of the incisura. Consequent to distension, the leaflets recoil because of their inherent elastic properties. This recoil decreases the volume of the root of the aorta and causes pressure to increase. Distension and recoil of a mounted porcine valve were shown to occur in early diastole by high speed cinematography (2,000 frames/sec).

If stretch and rebound of the aorta are responsible for the incisura as some workers[1,3,4] have indicated, the diameter of the aorta would need to increase during the rapid fall of pressure and to decrease during the subsequent rise of pressure associated with the dicrotic wave. However, this does not occur.[9] During the rapid decrease of pressure at the onset of the incisura there is a simultaneous reduction in the diameter of the aorta whereas during the dicrotic wave the diameter of the aorta increases.[9] The reduction of the aortic diameter coincident with the reduced pressure during the incisura would therefore seem to be related to distension of the aortic valve into the ventricle. The increased volume of the root of the aorta, required for a reduction of pressure, occurs by virtue of the expanded volume produced by the stretch of valve leaflets into the left ventricle. With nonphysiologic valves, as with rigid disc prosthetic valves, some characteristics of valve closure differ from those of normal or even diseased human valves. The disc closes later during ejection[8] and at a different time relative to retrograde flow, and the energy of impact at the time of closure may differ from that found in normal physiologic states or pathophysiologic conditions. With such nonphysiologic valves, factors may participate in the production of an apparent incisura that do not contribute to the incisura in patients with a normal or diseased valve.

The attribution of the aortic incisura to effects of compliance of the aortic wall may have risen from data

suggesting that backward flow at the end of systole is coincident with valve closure.[10] If this were true, this flow would increase the volume of the aorta, thereby distending it. The rebound of the aorta that would follow is credited with the production of the dicrotic wave.[4] This mechanism appears to be unlikely because the aortic incisura has been shown to occur 12 to 15 msec before the nadir of backward flow.[7,11] We[7] have observed that augmentation of forward or retrograde flow did not affect the magnitude of the aortic incisura.

Clinical implications: Variations of the magnitude of the aortic incisura in various aortic valve diseases can be explained in view of the mechanism of its production postulated in our study. The absence of the incisura in severe calcific aortic stenosis appears to be related to the absence of distensibility of the aortic valve, which results from thickening and calcification of the leaflets. Because little or no stretch or recoil can occur, no variations of pressure are produced. In aortic insufficiency, the failure of the valve to close completely results in inability of the valve to distend into the left ventricle. Again, this causes a negligible incisura. In congenital aortic stenosis, the leaflets are fused but retain their flexibility and distensibility. These characteristics allow the valve to balloon into the left ventricle during early diastole and permit an appreciable recoil.

The physiologic principles relating to the valve origin of the incisura therefore may be applied clinically. A prominent aortic incisura implies that the aortic valve is normally distensible. A reduction of the amplitude of the aortic incisura implies malfunction of the aortic valve. An absent or reduced aortic incisura, in view of our findings, offers physicians another indicator of aortic valve disease.

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Myocardial Scintigraphy With Technetium-99m Pyrophosphate During the Early Phase of Acute Infarction

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To determine the sensitivity of myocardial scintigraphy with technetium-99m pyrophosphate during the early phase of acute myocardial infarction, 31 patients admitted to the coronary care unit with prolonged ischemic pain underwent imaging within 4 to 8 hours and again at 24 hours after the onset of symptoms. In 11 of 15 patients with documented acute myocardial infarction, increased focal myocardial uptake was demonstrated on early myocardial scintigraphy. Focal uptake was observed in only 2 of 16 patients with unstable angina pectoris. Three of four patients with normal early scintigrams had massive transmural myocardial infarction. Normal early scintigrams in these three patients may have reflected poor perfusion because the images were abnormal at 24 hours. In four patients the extent of technetium-99m pyrophosphate uptake increased more than 20 percent at 24 hours without other evidence of infarct extension. In the other seven patients, there was no significant change in the area of the abnormal radioactive uptake between early and delayed scintiscans. This study suggests that technetium-99m pyrophosphate scintigraphy can detect acute myocardial infarction as early as 4 hours after the onset of symptoms although the sensitivity rate (73 percent) is less than that at 24 hours.

Scintigraphic techniques using infarct-avid radiotracers provide a direct method for determining the extent of acute myocardial infarction.[1–3] Previous investigators[4] have suggested that 12 hours is the earliest time after the onset of symptoms for accurate detection of infarction. With the advent of therapeutic maneuvers aimed at limiting the extent of myocardial necrosis,[5] it has become increasingly important to measure infarct size accurately during the early phase of acute infarction. We have, therefore, determined the accuracy of myocardial scintigraphy with technetium-99m pyrophosphate for detecting acute infarction and predicting its size in the first hours after onset of symptoms.

Methods

Myocardial scintigraphy using technetium-99m pyrophosphate was performed in 31 patients admitted to the coronary care unit with suspected acute myocardial infarction. Patients were selected for study only if they had a clearly defined onset of precordial chest pain occurring no more than 8 hours before imaging, an uncomplicated course during the first 24 hours after admission and no previously documented myocardial infarction.

Patients: *Acute myocardial infarction was diagnosed if the following three criteria were met:* (1) a history of typical chest pain lasting 1 hour or more, (2) the presence of a characteristic pattern of elevation in the creatine kinase (CK) serum activity above normal levels with subsequent resolution, and (3) appearance of Q waves (transmural infarction) or evolution of ST-T wave changes (nontransmural infarction) characteristic of infarction in the electrocardiogram.

From the Departments of Radiology and Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts. This study was supported in part by Grants GM 18674 and HL 17739 and Contract NO1 HV 53000 from the U.S. Public Health Service, Bethesda, Maryland, and by Grant 75 796 from the American Heart Association, Dallas, Texas. Manuscript received February 28, 1977; revised manuscript received July 1, 1977, accepted July 6, 1977.

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TABLE I

Summary of Findings in 15 Cases of Acute Myocardial Infarction

Case no.	Early Scintigraphy 4–5 Hr	Early Scintigraphy 6–8 Hr	Change in ^{99m}Tc PYP* Uptake (%)	CK†	Peak CK‡ (IU/liter)	Location of Infarction: Transmural	Location of Infarction: Non-transmural
1	+	...	+4.8	−	1060	Anterior	...
2	+	...	−1.6	−	190	...	Anterior
3	+	...	−6.3	−	2766	Posterolateral	...
4	+	...	−7.6	−	1950	Inferior	...
5	...	+	+2.1	−	624	...	Apical
6	...	+	+21.0	+	246	...	Inferior
7	...	+	+3.3	+	728	Lateral	...
8	...	+	+45.8	+	3250	Anterolateral	...
9	...	+	+33.8	+	574	...	Anteroseptal
10	...	+	+1.8	+	524	Inferior	...
11	...	+	+33.6	+	532	Inferior	...
12	...	−	...	+	1104	Posterior	...
13	−	...	...	−	4540	Anterolateral	...
14	...	−	...	+	354	Anterolateral§	...
15	...	−	...	+	5000	Anterolateral¶	...

* Percent change in area of uptake between early and delayed scintigraphy.
† Serum creatine kinase at time of early scintigraphy.
‡ Normal value: 50 to 180 IU/liter.
§ Patient died within 24 hours of infarction.
¶ Patient died within 3 days of infarction.
+ = abnormal; − = normal; ^{99m}Tc PYP = technetium-99m pyrophosphate.

Unstable angina pectoris was defined as prolonged chest pain, ischemic in character and of recent onset (less than 1 month), that had increased in frequency, severity or duration in the month before admission. Patients with this diagnosis had no electrocardiographic evidence of acute myocardial infarction and a peak serum CK value in the 3 days after admission that was less than the upper limit of normal.

Fifteen of the 31 patients had an acute myocardial infarction that was transmural in 11 and nontransmural in 4, as judged from electrocardiographic changes. The remaining 16 patients had unstable angina pectoris. Scintigraphy was performed in all patients within 4 to 8 hours after the onset of chest pain.

Myocardial scintigraphy: The procedure was performed as soon as possible after the patients' admission to the coronary care unit and was repeated 24 hours later. Imaging was performed 90 minutes after the administration of 10 mCi (5 mg) of technetium-99m pyrophosphate using an Anger scintillation camera with a low energy all purpose collimator and a pulse height analyzer window peaked symmetrically over the 140 kev photopeak of technetium-99m. Imaging was performed in the anterior, left anterior oblique and left lateral projections, collecting 400,000 counts in each view. The scintigraphic images were obtained on Polaroid® film (type 52) and were interpreted independently by two observers without prior knowledge of the clinical diagnosis. The extent of technetium-99m pyrophosphate uptake was measured from the anterior projection with use of planimetry in the patients with documented acute myocardial infarction. (The borders of the focal myocardial uptake were obscured by overlying osseous activity in the left anterior oblique and left lateral views. These projections were therefore not used to measure infarct size.) The percent change in the area of the myocardial uptake between 4 and 24 hours was then determined.

The reproducibility of the planimetric measurement was assessed in four control patients with acute infarction. Repeat scintigraphy was performed in the anterior position after the camera detector was repositioned. The area of technetium-99m pyrophosphate uptake in each of the two anterior views was measured with planimetry.

Results

Myocardial infarction: In 11 of the 15 patients with acute infarction (Patients 1 to 11, Table I), increased focal myocardial activity was demonstrated on early myocardial scintigraphy. In all cases, myocardial uptake was less intense in early scintigrams (4 to 8 hours) than in the 24 hour study. In 5 of the 11 (Cases 1 to 5), serum CK activity was within normal limits at the time scintigraphy was performed (Fig. 1).

In one case (Patient 12), diffuse myocardial uptake was evident on early scintigraphy performed 90 minutes after injection. Results of repeat scintigraphy 3 hours after injection were normal, suggesting that the initial diffuse uptake was caused by blood pool activity.

In the other three patients (Cases 13 to 15) with normal myocardial scintigrams, imaging was performed 4 hours (one patient) and 8 hours (two patients) after the onset of pain. In one patient (Case 13), serum CK was within normal limits at the time of imaging. All three patients had a massive transmural myocardial infarction. Two of these patients (Cases 14 and 15) died of pump failure within 1 week of infarction, and the third patient's course was complicated by cardiogenic shock. Subsequent scintigrams were abnormal in the two patients surviving 24 hours after infarction.

Unstable angina pectoris: Of the 16 patients with unstable angina pectoris, 12 had normal early scintigrams. Of the remaining four patients, two had focal and two had diffuse myocardial uptake (Table II). With use of focal myocardial uptake as the criterion for the diagnosis of acute myocardial infarction, the sensitivity

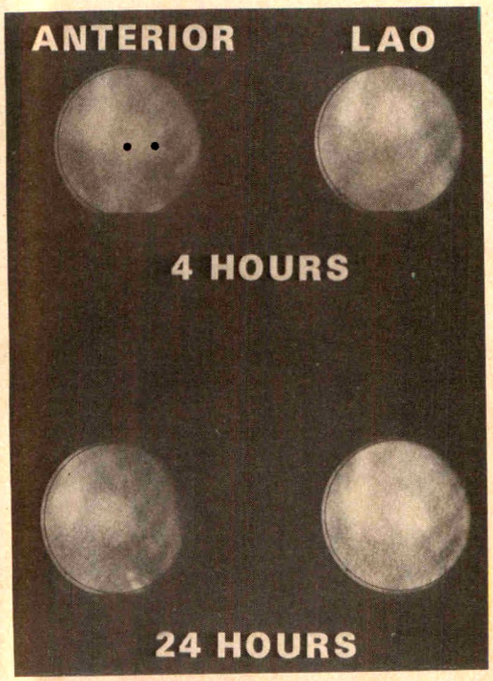

FIGURE 1. Case 1 (Table I). Scintigraphy performed with technetium-99m pyrophosphate in the anterior and left anterior oblique (LAO) projections 4 hours **(upper panel)** and 24 hours **(lower panel)** after the onset of symptoms in a patient with acute anteroseptal myocardial infarction. The serum CK level was normal at 4 hours.

rate of early scintigraphy was 73 percent and the specificity rate 88 percent.

Reproducibility: In the four control patients with documented myocardial infarction who underwent imaging twice in the anterior position, the percent change in area between the first and second measurements was 5.3 ± 1.2 percent (mean ± standard error of the mean). The change in area of the abnormal radioactive uptake between early and delayed scintiscans in 7 of the 11 patients with early focal myocardial uptake was not significantly different from the results obtained in testing the reproducibility of the method (Table I). The area of technetium-99m pyrophosphate uptake increased in eight patients between early and delayed scintigraphy. In four of these eight patients, the increase was greater than 20 percent. The area decreased slightly in the remaining three patients.

Discussion

Acute myocardial infarction can be detected with technetium-99m pyrophosphate within 4 hours of the onset of chest pain and before elevation of serum creatine kinase activity. The detection rate is somewhat lower with early compared with delayed (24 hours to 7 days) scintigraphy.[4,6] However, three of the four patients with normal early scintigraphy in this study had massive transmural infarcts and did not present diagnostic problems on admission. The specificity rate of

TABLE II

Summary of Scintigraphic Results in 31 Cases

Early Myocardial Scintigraphy	Diagnosis (no. of patients)	
	Acute Myocardial Infarction	Unstable Angina Pectoris
Normal	4 (27%)	12 (75%)
Diffuse uptake	0	2 (12.5%)
Focal uptake	11 (73%)	2 (12.5%)
Total patients	15	16

early scintigraphy was high, with normal or diffuse patterns observed in 88 percent of patients with unstable angina pectoris. Of course, we cannot rule out the possibility that focal uptake of technetium-99m in two patients with unstable angina pectoris actually represented an area of myocardial necrosis.

The failure of massive infarcts to concentrate pyrophosphate early is analogous to the normal scintigrams obtained in a canine model of infarction 7 hours after permanent coronary occlusion; in animals subjected to temporary occlusion, early scintigraphy was abnormal.[7] Because pyrophosphate uptake is flow-limited, large infarcts receive insufficient tracer to be detected with early scintigraphy. That delayed scintigraphy is abnormal in these patients suggests that the initial marked reduction in flow is followed by rapid establishment of collateral flow.

Estimating changes in extent of infarction: The substantial increase in size of the technetium-99m pyrophosphate uptake in four patients may indicate some extension of the infarct during the first 24 hours; this could not be confirmed by other criteria. Thus, the extent of technetium-99m pyrophosphate uptake appears time-dependent in at least some patients with acute infarction without other evidence of reinfarction. For myocardial scintigraphy to be useful in estimating changes in the size of infarction, the time interval between infarction and scintigraphy will have to be known and serial scintigraphy will probably be necessary. In any case, the extent of infarction can probably be determined as early as 4 hours after the onset of symptoms (assuming that there is good correlation between infarct size and tracer uptake)[7–12] although prediction of ultimate size cannot be made in many patients.

Currently no other technique is available that accurately measures the size of acute infarction during the early period, 4 to 8 hours, after the onset of symptoms. Creatine kinase clearance curves require 10 to 12 hours before accurate sizing is possible.[13] Use of myocardial perfusion scintigraphy with potassium analogs and measurements of wall motion abnormalities with radionuclide techniques cannot distinguish between alterations in function due to the acute process, ischemia or old infarction.[14] S-T segment mapping provides a qualitative index of the size of infarction and can signal directional changes in the size of the evolving infarct, but it cannot quantitate the degree of necrosis.[15]

Implications: Although infarct scintigraphy may

estimate infarct size in most cases within 8 hours of symptoms, technetium-99m pyrophosphate uptake may not reflect the degree of necrosis within the borders of the infarct. The uptake of the radiotracer in any given tissue section is related not to the degree or amount of infarction but only to the presence of necrosis.[7,8] As a result, the border zone of the infarct may concentrate pyrophosphate in small nests of necrotic tissue interspersed between zones of reversibly ischemic tissue which can be salvaged by early treatment. Conversely, at the time of early scintigraphy, the tracer may be concentrating in ischemic tissue destined for ultimate necrosis but potentially salvageable with appropriate interventions.[16] Thus, the use of early scintigraphy to provide a quantitative measure of the efficacy of drug therapy will require a clearer understanding of the mechanism of technetium-99m pyrophosphate localization.

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Thallium-201 Myocardial Perfusion Scintigraphy for the Clinical Clarification of Normal, Abnormal and Equivocal Electrocardiographic Stress Tests

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Sixty-five patients were studied with stress electrocardiography and thallium-201 relative myocardial perfusion scintigraphy. Results were correlated with selective coronary angiography. Scintigraphy was more sensitive (85 versus 67 percent), more specific (89 versus 63 percent) and significantly more accurate (87 versus 65 percent) than stress electrocardiography for the diagnosis of significant coronary arterial lesions in patients with isoelectric S-T segments at rest. Stress scintigraphy helped clarify the equivocal stress test due to left bundle branch block, left ventricular hypertrophy, drugs, hyperventilation and other conditions and was more accurate than the stress electrocardiogram (89 versus 53 percent) even in the presence of a depressed S-T segment at rest. Thallium-201 scintigraphy is a safe and simple noninvasive method for identifying abnormal myocardial perfusion, stress-induced ischemia and, indirectly, significant coronary arterial lesions.

Methods for the noninvasive diagnosis and evaluation of coronary artery disease have been dramatically advanced by the development of relative myocardial perfusion scintigraphy.[1–3] During the last 5 years, a variety of radionuclides, including potassium-43, cesium-129, cesium-131 and rubidium-81, have been used to identify abnormalities of myocardial perfusion, regions of stress-induced ischemia and, indirectly, significant coronary arterial lesions.[2–8] Investigators have demonstrated the ability of scintigraphic methods to identify the false positive treadmill test[9] and have shown its increased sensitivity and specificity for the identification of coronary arterial disease.[2,3] Thallium-201 is a cyclotron-produced radionuclide with a small energy of emission and a 73 hour physical half-life. The intramyocardial distribution of thallium-201, similar to that of other intracell cations, has been shown to correlate with coronary blood flow after an intravenous injection.[10] Other determinants of thallium-201 distribution include the presence of myocardial scar and, possibly, altered membrane function of any cause.[11] Extracted 70 to 80 percent by the coronary circulation on its first pass,[12] thallium-201 maintains its initial localization for approximately 1 hour before gradual redistribution occurs.[13] Its rapid blood clearance, intramyocardial localization and physical characteristics make it the most promising agent now available for myocardial perfusion scintigraphy. To evaluate its clinical utility, we performed relative myocardial perfusion scintigraphy with thallium-201 in patients undergoing selective coronary angiography.

Methods

Perfusion scintigrams and stress electrocardiograms were correlated with selective coronary angiograms in 74 patients evaluated for the presence of coronary disease. All patients were referred for evaluation of chest pain suspected to be coronary in origin. None had pain at rest, but 19 had electrocardiographic Q waves 0.04 second or more in duration, confirming a history of prior myocardial infarction.

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Procedure: After a baseline 12 lead electrocardiogram, an intravenous catheter was placed in the forearm and each patient underwent maximal graded treadmill stress testing until limiting symptoms prevented continuation according to a modified Bruce protocol.[14] One minute before the exercise end point was reached, 2 mCi of thallium-201 (supplied by New England Nuclear, Boston, Massachusetts) was injected through the established intravenous line. The blood pressure and a modified V_5 electrocardiographic lead were monitored during standing, hyperventilation, exercise and a 6 to 8 minute recovery period. After recovery, scintigraphy was performed with a Searle Pho Gamma IV scintillation camera. To ensure adequate evaluation of relative myocardial radioactivity, an image was taken to 200,000 counts in the anterior projection and the time noted. This was followed by images in the 45° left anterior oblique and left lateral projections, taken to equal time. All scintigrams were performed using a converging collimator, and a 20 percent window was centered at approximately 75 kev. Hepatic or splenic activity was shielded when apparent. Patients with normal stress images had no scintigraphic evidence of stress-induced coronary malperfusion or significant coronary arterial narrowing and were not restudied at rest. Patients with abnormal stress images were restudied, usually within 1 week of the initial stress scintigram. All scintigrams were performed with the patient's informed consent and in a fasting state. Always within 2 weeks and often within 48 hours of the scintigraphic study the patient underwent selective coronary angiography with use of the Sones or Judkins technique and multiple orthogonal projections.

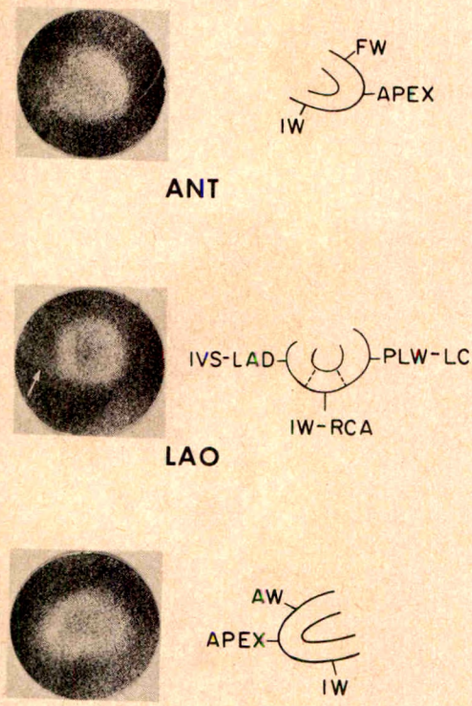

FIGURE 1. Normal thallium-201 myocardial perfusion scintigram in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections performed after peak treadmill stress in a patient with normal coronary arteries on angiography. Myocardial uptake in the left ventricle is intense and homogeneous. There is vague evidence of right ventricular activity in this example **(arrow).** The right ventricle occasionally appears as a region of faint activity anterior to the left ventricle. The diagram to the right of each image indicates ventricular as well as coronary anatomy. AW = anterior wall; FW = free wall; IVS = interventricular septum; IW = left ventricular inferior wall; LAD = distribution of the left anterior descending coronary artery; LC = common region of distribution of the left circumflex coronary artery; PLW = left ventricular posterior lateral wall; RCA = common distribution of the right coronary artery.

Interpretation of stress electrocardiograms, scintigrams and coronary angiograms: *The treadmill electrocardiogram* was considered abnormal and positive for ischemia and significant coronary artery disease if 1 mm or greater horizontal or downsloping S-T segment depression beyond an isoelectric baseline, 0.08 mm from the J point, appeared during exercise or in recovery. It was called equivocal for the diagnosis of ischemia, regardless of the degree of exercise-induced S-T depression, if the baseline S-T segment was depressed more than 1 mm. Such equivocal tests were also analyzed to determine the reliability of stress-induced S-T segment depression 1 mm below the baseline. The treadmill test was never stopped because of a specific target heart rate but negative treadmill tests in which the patient failed to reach 85 percent of the maximal predicted heart rate for age were classified as suboptimal studies.

A scintigraphic defect at rest was interpreted as evidence of prior infarction. However, only the stress scintigram with new or increased abnormalities beyond those seen at rest was considered indicative of reversible relative hypoperfusion and judged a positive study consistent with stress-induced myocardial ischemia. Stress-induced abnormalities were localized to myocardial regions and to the coronary vessels perfusing these regions.

Coronary angiograms were performed in multiple projections. Significant coronary lesions were those revealing a 75 percent or greater area of stenosis in the course of a major coronary vessel on selective coronary angiography.

Stress electrocardiograms, scintigrams and coronary angiograms were read by separate and independent observers, each without knowledge of the results of the other studies. The initial 50 scintigrams were read a second time to determine the reproducibility of image interpretation.

The ability of the stress electrocardiogram and scintigram to diagnose stress-induced ischemia and, indirectly, significant coronary stenosis was compared. Evidence of prior infarction in the resting electrocardiogram or scintigram is not in itself evidence of ongoing ischemia and was not taken as evidence of ongoing stress-induced ischemia in this study. Although commonly related to significant coronary lesions, neither significant electrocardiographic Q waves nor scintigraphic abnormalities at rest were of themselves accepted as findings positive for ischemia.

Results

Overall findings: Figure 1 shows a normal thallium-201 perfusion study with an accompanying diagram to clarify the scintigraphic anatomy. Stress-induced abnormalities involving the interventricular septum were interpreted as due to left anterior descending coronary artery disease; those involving the posterior lateral left ventricular wall were related to left circumflex coronary artery disease and inferior wall abnormalities were related to right coronary stenosis. Apical lesions could be the result of distal disease in any of the vessels and could be localized only in the presence of other accompanying scintigraphic abnormalities.

Nine patients, seven with significant coronary lesions, had no stress-induced electrocardiographic or scintigraphic abnormalities at suboptimal stress. None of these patients achieved 85 percent of the maximal predicted heart rate for age and it is possible that both tests in these nine patients were negative because of the suboptimal nature of the stress alone. These patients, four with prior infarction, were excluded from further analysis.

Sixty-five patients were studied at optimal stress or had stress-induced electrocardiographic or scintigraphic abnormalities at a suboptimal heart rate (Fig. 2). There were 48 men and 17 women with a mean age of 52 years (range 19 to 69 years). Twenty-five patients had an abnormal stress electrocardiogram, 21 a normal stress electrocardiogram and 19 an equivocal stress electrocardiogram with depressed S-T segments at rest. The latter were due to left bundle branch block in two patients, left ventricular hypertrophy in six patients, digitalis in five patients and hyperventilation in three patients; they were of unknown cause in three patients. Three patients with right bundle branch block were studied and were included in the group with normal resting S-T segments.

Positive stress electrocardiogram: Among the 25 patients with a stress electrocardiogram positive for ischemia, 17, all with significant coronary lesions on coronary angiography, had an abnormal scintigram revealing stress-induced changes. Eight of the 25 patients had a normal stress scintigram, including 7 without significant coronary lesions on angiography. Among these seven, three had chest pain in association with mitral valve prolapse, but the cause of the chest pain in all seven was unclear. One patient with a prior infarction showed no change in scintigraphic perfusion in spite of exercise-induced ischemic S-T segment depression. Figure 3 demonstrates the scintigraphic study of a patient with stress-induced abnormalities involving the left ventricular septum, apex and inferior wall. The scintigram performed 6 days later at rest revealed a normal homogeneous perfusion pattern. The electrocardiogram, suggestive of ischemia during stress, became definitely abnormal in recovery but failed to give localizing information. Angiography revealed significant lesions of the left anterior descending and right coronary arteries. Figure 4 demonstrates the normal stress scintigram of a patient with chest pain and an abnormal stress electrocardiogram. The stress electrocardiogram is said to be a false positive study in this case only with reference to its relation to the normal coronary angiogram.

Negative stress electrocardiogram: Among the 21 patients with a stress electrocardiogram negative for ischemia, 13 had a normal stress scintigram; in 3 patients both tests were negative despite the presence of a significant coronary lesion on angiography. However, eight patients with a negative stress electrocardiogram had a positive stress scintigram; six of the eight had significant coronary lesions. Two patients with a negative stress test and no coronary lesions had apparent

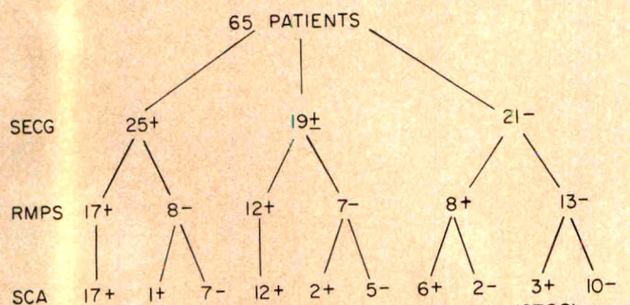

FIGURE 2. Overall results of stress electrocardiography (SECG), regional myocardial perfusion scintigraphy (RMPS) and selective coronary angiography (SCA) in 65 patients. Scintigraphy was more accurate than stress electrocardiography in identifying the presence of significant coronary artery disease. Additionally, the scintigram clarified the equivocal stress electrocardiogram. + = an abnormal study; − = a normal study; ± = an equivocal study.

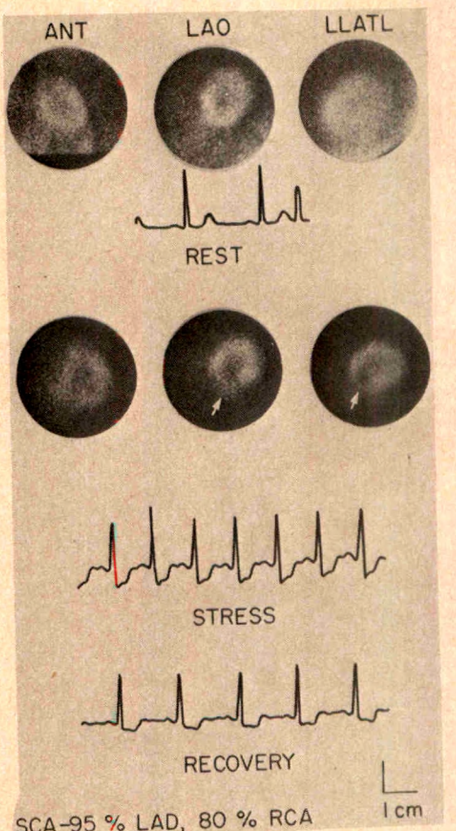

FIGURE 3. Abnormal stress electrocardiogram and scintigram. Resting **(top)** and stress **(bottom)** electrocardiogram and thallium-201 scintigram in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections performed in a patient whose selective coronary angiograms (SCA) demonstrated significant left anterior descending (LAD) and right coronary artery (RCA) lesions. The image at rest is normal; that during stress shows significant abnormalities involving the left ventricular apex and inferior wall and distal aspect of the interventricular septum **(arrows).** Although both the stress electrocardiogram and scintigram predicted the presence of significant coronary lesions, only the scintigram gave accurate localizing information.

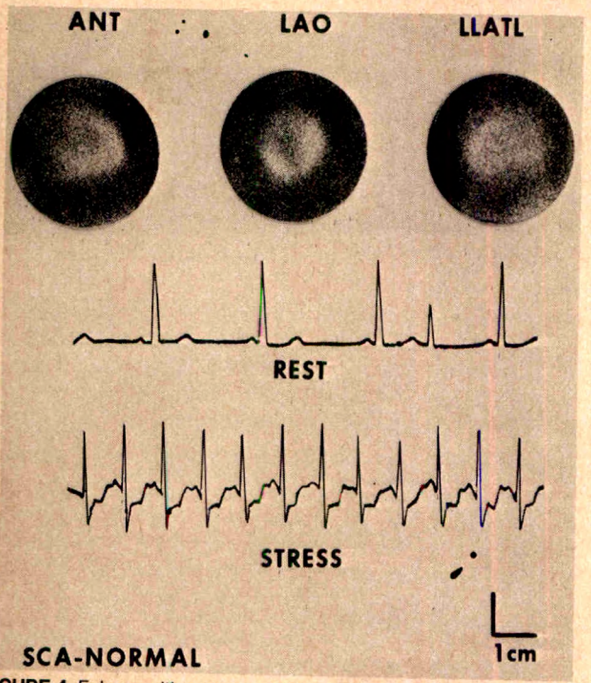

FIGURE 4. False positive stress electrocardiogram. Stress thallium-201 perfusion images in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections **(top)** and the resting and stress electrocardiograms **(bottom)** in a patient with normal coronary arteries on angiography (SCA). Radionuclide distribution was normal but the stress electrocardiogram showed distinct and significant horizontal S-T segment depression. Scintigraphy proved to be the valid clinical indicator.

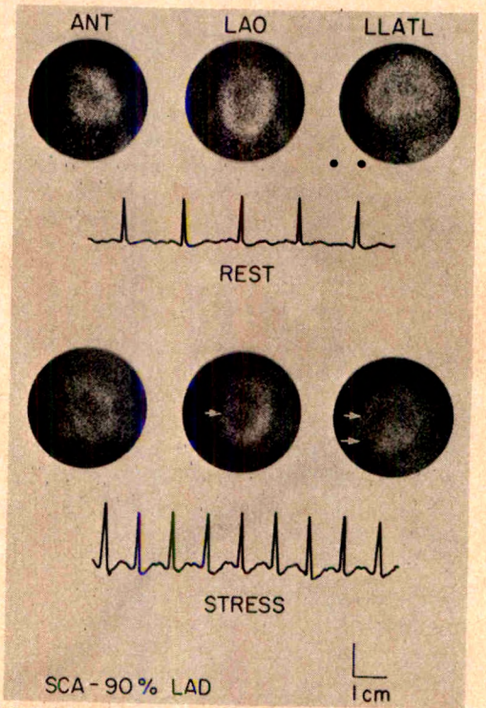

FIGURE 5. False negative stress electrocardiogram. Resting **(top)** and stress **(bottom)** electrocardiogram and thallium-201 perfusion images in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections in a patient whose selective coronary angiograms (SCA) demonstrated significant left anterior descending coronary artery disease. The resting scintigram reveals homogeneous radioactivity. With stress, the interventricular septum and anterior left ventricular wall **(arrows)**, the regions supplied by the stenotic vessel, are barely visible. The electrocardiogram shows no ischemic change on exercise.

stress-induced image abnormalities. One of these had a diffuse cardiomyopathy and an abnormal resting image; the other had no documented heart disease and a normal resting image. Four patients with a negative stress electrocardiogram at suboptimal stress had a positive stress scintigram and significant coronary lesions. No other patients had a positive scintigram at suboptimal stress. Figure 5 demonstrates an abnormal stress scintigram and a normal or false negative stress electrocardiogram in a patient with severe left anterior descending coronary artery disease. Although the distribution of radioactivity was essentially homogeneous at rest, the anterior and septal left ventricular walls show relatively decreased intensity during stress consistent with relative perfusion deficits in these regions.

Table I compares the sensitivity, specificity and accuracy of stress electrocardiography with that of relative myocardial perfusion scintigraphy in the diagnosis of significant coronary artery disease in the 46 patients with resting isoelectric S-T segments. Scintigraphy was more sensitive (85 versus 67 percent) and more specific (89 versus 63 percent) than stress electrocardiography, but because of the small number of patients studied neither difference was statistically significant at the 0.05 level. Overall, the scintigraphic method permitted the correct angiographic diagnosis much more frequently than the stress electrocardiogram, even in the presence of resting isoelectric S-T segments. The scintigraphic accuracy rate was 87 percent compared with 65 percent for stress electrocardiography (difference significant at the 0.05 level).[15] Significant coronary artery disease was present in all patients having both an abnormal stress electrocardiogram and an abnormal scintigram.

Equivocal stress electrocardiogram: Nineteen patients had a stress electrocardiogram with abnormal S-T segments at rest. Among these 19 patients, 12 with stress-induced scintigraphic abnormalities had significant coronary arterial lesions on angiography. The other seven patients had normal stress perfusion images; five of these had no angiographic evidence of coronary disease, but two had significant coronary lesions. Figure 6 illustrates the equivocal stress electrocardiogram in a patient taking digoxin. The scintigraphic study is grossly abnormal with new stress abnormalities involving the left ventricular inferior wall, the distal aspect of the posterior lateral wall, the interventricular septum and the apex. In the presence of drug-related S-T segment depression at rest, the scintigram clearly documented significant left anterior descending and right coronary artery disease and suggested probable left circumflex coronary artery disease. This patient's

TABLE I

Analysis of Results of Relative Myocardial Perfusion Scintigram Versus Stress Electrocardiogram (SECG)

Sensitivity Matrix

Scintigram	Stress Electrocardiogram TP	FN
TP	17	6
FN	1	3

Sensitivity: SECG = 0.67; scintigram = 0.85
$0.10 > P > 0.05$

Specificity Matrix

Scintigram	Stress Electrocardiogram TN	FP
TN	10	7
FP	2	0

Specificity: SECG = 0.63; scintigram = 0.89
$0.20 > P > 0.10$

Accuracy Matrix

Scintigram	Stress Electrocardiogram TP + TN	FP + FN
TP + TN	27	13
FP + FN	3	3

Accuracy: SECG = 0.65; scintigram = 0.87
$0.05 > P > 0.02$

A true positive test (TP) refers to abnormal electrocardiographic or scintigraphic studies performed in patients with documented significant coronary lesions. A true negative test (TN) refers to a normal electrocardiographic or scintigraphic study in patients with documented normal or insignificantly narrowed coronary arteries. A false positive test (FP) refers to an abnormal electrocardiographic or scintigraphic study in patients with documented normal or insignificantly narrowed coronary arteries. A false negative test (FN) refers to a normal electrocardiographic or scintigraphic study in patients with documented significant coronary lesions. In evaluating our results only the findings in 46 patients with a definitely positive or definitely negative stress electrocardiogram could be compared with the results of scintigraphy. The 27 patients with a positive coronary angiogram are considered under the sensitivity matrix, whereas the 19 with a negative coronary angiogram are considered under the specificity matrix. The accuracy matrix attempts to evaluate simultaneously sensitivity and specificity and is a compilation of the preceding two matrixes. Results were analyzed with use of McNemar's test[15] (see text).

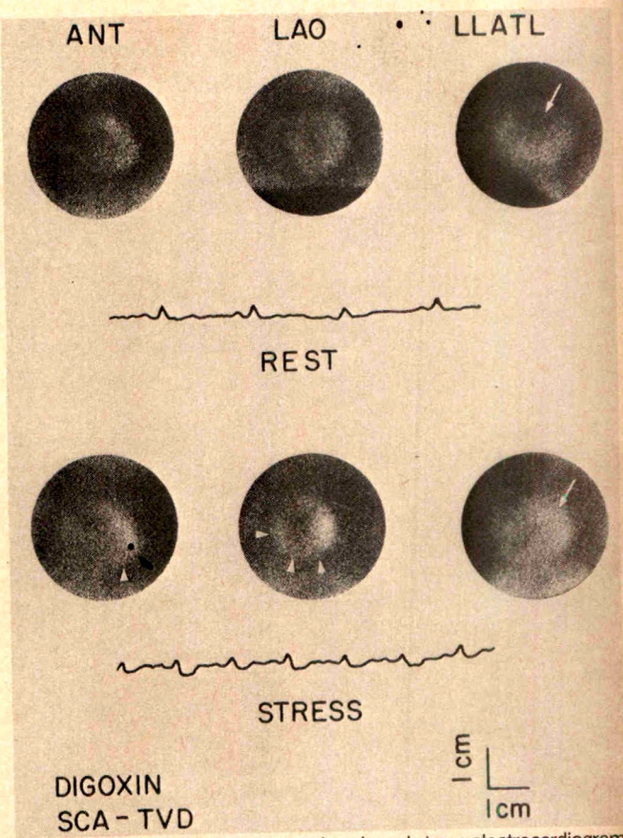

FIGURE 6. Abnormal scintigram and equivocal stress electrocardiogram in a patient with coronary artery disease. Resting **(top)** and stress **(bottom)** electrocardiogram and scintigram in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections in a patient whose coronary angiograms (SCA) revealed severe triple vessel disease (TVD). The patient was taking digoxin. The electrocardiogram showed S-T segment depression at rest that became somewhat deeper during stress. Such drug-related S-T segment depression made interpretation of the electrocardiogram difficult. However, the image showed clear stress-induced perfusion abnormalities involving the left ventricular inferior wall, distal aspect of the posterior lateral wall, interventricular septum and apex **(arrow points)** attesting to the severity and extent of coronary disease documented angiographically. The redistribution of radioactivity is also prominent in the left lateral projection where the regions of the ventricular base and lateral wall, relatively unlabeled at rest, become the most intense regions with stress **(arrows)**, indicating "best" perfusion of the basal or proximal aspects of the ventricle and widespread distal abnormalities. The perfusion scintigram clarified the equivocal stress electrocardiogram.

coronary angiogram revealed triple vessel disease. Figure 7 illustrates the resting and stress electrocardiogram and scintigram in a patient with severe left ventricular hypertrophy. Again, conduction abnormalities associated with left ventricular hypertrophy made electrocardiographic interpretation hazardous. The stress scintigram was entirely normal in this patient with normal coronary arteries. Another patient (Fig. 8) had an abnormally depressed resting electrocardiographic S-T segment and a history of atypical chest pain. The stress electrocardiogram showed significant S-T segment depression, but definite interpretation was difficult because of the abnormality at rest. The stress scintigram clearly shows new perfusion abnormalities in the region of the left ventricular posterior lateral wall, the septum and the apex, indicating significant lesions in the left anterior descending and left circumflex coronary arteries. The region supplied by the right coronary artery shows the best relative perfusion. Coronary angiography revealed severe triple vessel disease.

When the 19 equivocal tests were further analyzed, 9 of the 12 patients with significant coronary lesions had further stress-induced S-T segment depression of 1 mm or more; however, 6 of the 7 patients without significant coronary lesions also had such stress-induced S-T changes. In this latter group, the scintigram tended to demonstrate greater specificity than the stress electrocardiogram, but the trend was not significant because of the small number of patients studied. However, when the total of 19 patients was considered, the stress scintigram again predicted the correct angiographic diag-

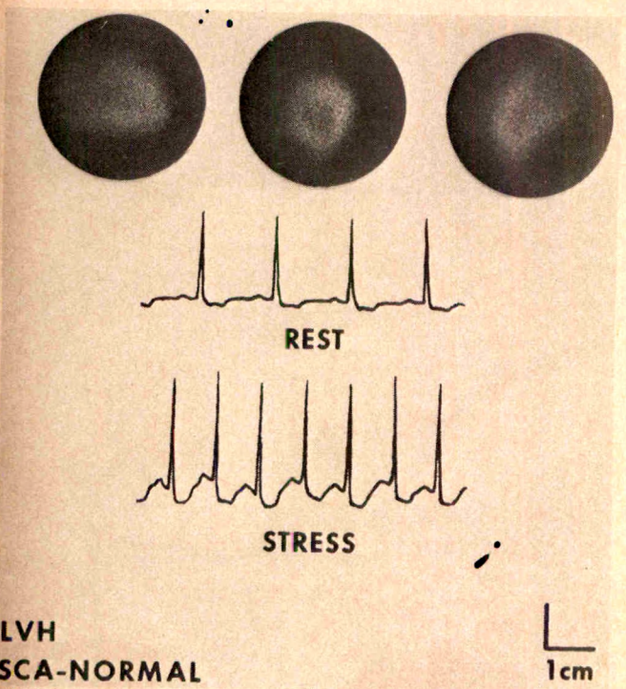

FIGURE 7. Normal scintigram and equivocal stress electrocardiogram in a patient with normal coronary arteries on angiography (SCA). Resting **(top)** and stress **(bottom)** electrocardiogram and stress scintigram in the anterior **(left),** left anterior oblique **(center)** and left lateral **(right)** projections in a patient with troublesome atypical chest pain and a history of hypertension. The full resting electrocardiogram revealed severe left ventricular hypertrophy (LVH). The monitored lead showed S-T segment depression that deepened with stress and was difficult to interpret in view of the depression at rest. The perfusion image was normal and clarified the stress electrocardiogram.

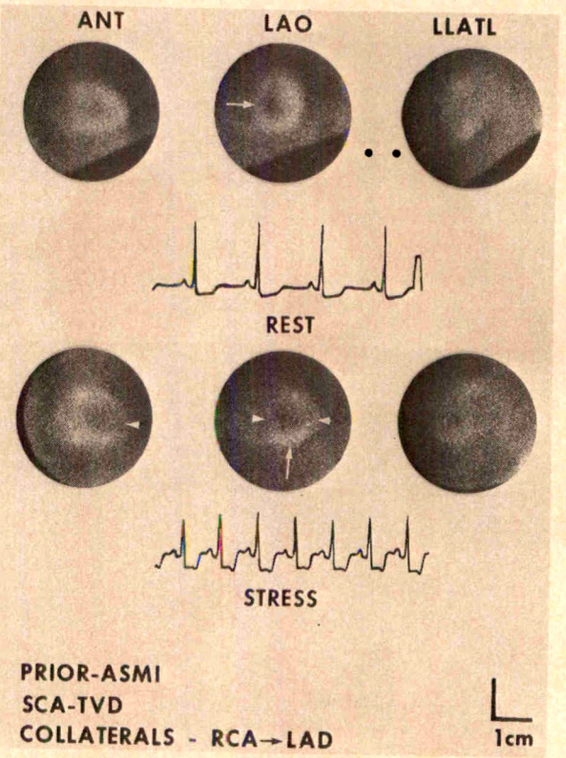

FIGURE 8. Perfusion scintigram and triple vessel disease. Resting **(top)** and stress **(bottom)** electrocardiogram and scintigram in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections in a patient with atypical chest pain. The resting scintigram showed subtle diminution in relative septal activity suggestive of a prior anteroseptal myocardial infarction (ASMI) in this region **(arrow).** Radionuclide distribution changed drastically with stress, exposing gross abnormalities of the left ventricular posterior lateral walls, septum and apex **(arrow points).** The study is consistent with severe coronary disease and stress-induced malperfusion involving at least two vessels, the left anterior descending and the left circumflex coronary arteries. The region of right coronary perfusion appears "best" perfused **(vertical arrow in stress scintigram).** Because this is a relative study, it is not necessarily true that the region of "best" perfusion is the region of normal perfusion. Here, the right coronary artery had severe localized stenosis in the presence of severe triple vessel disease (TVD). The stress electrocardiogram was difficult to interpret in the presence of resting S-T segment abnormalities in this patient taking digoxin. Abbreviations as in Figure 3.

nosis more frequently than the stress electrocardiogram. The scintigraphic accuracy rate of 89 percent was significantly better ($P < 0.05$) than the 53 percent accuracy rate of the stress electrocardiogram in patients with S-T segment depression at rest.[15]

Prior myocardial infarction: Forty-one of the 65 patients studied had significant coronary artery disease, including 15 with documented historical and electrocardiographic evidence of prior transmural infarction. All 15 patients with prior infarction had an abnormal resting scintigram, and 12 of these had new stress-induced image abnormalities that in 8 were in regions remote from the site of infarction. The stress electrocardiogram was abnormal in 7 of these 12 patients, equivocal in 3 and normal in 2. One patient with prior infarction had stress-induced electrocardiographic abnormalities in the absence of stress-induced scintigraphic change.

Scintigraphic localization, overall sensitivity and reproducibility: Correlation of the location of image abnormalities with the coronary anatomy was excellent. Scintigraphic defects corresponded well with the distribution of coronary arterial lesions. With one exception, all patients who had a significant scintigraphic septal abnormality had left anterior descending coronary artery disease; the single exception had significant stenosis in a dominant right coronary artery. Except in the two patients with a false positive scintigram, inferior wall abnormalities were always associated with right coronary arterial lesions and posterior lateral wall abnormalities were always associated with left circumflex lesions.

Although the presence of a perfusion defect on scintigraphy correlated well with a stenotic lesion in the appropriate coronary artery, the absence of a perfusion defect in a given myocardial region did not exclude a coronary lesion in the vessel perfusing that segment, especially in patients with multivessel disease. The image identified lesions in only 41 of 89 significantly affected vessels (46 percent). Thus, although scintigraphic sensitivity identified the presence of coronary

disease in a given patient, it did not identify all sites of coronary involvement.

Our results according to the degree of arterial involvement are shown in Table II. Among the 65 patients studied, 41 had significant coronary arterial lesions, including 8 with single, 18 with double and 15 with triple vessel disease. The scintigram was abnormal in 6 of 8 patients (75 percent) with single vessel disease, 16 of 18 patients (88 percent) with double vessel disease and 13 of 15 patients (86 percent) with triple vessel disease. If one excludes the 19 patients with an equivocal stress test, the stress electrocardiogram was abnormal in 1 of 4 patients (25 percent) with single vessel disease, 10 of 14 patients (71 percent) with double vessel disease and 7 of 9 patients (77 percent) with triple vessel disease.

Fifty scintigrams were interpreted by the same reader in a blinded fashion for a second time. There was total agreement with the initial reading in 45 cases (90 percent). Differences in interpretation in the other five cases were generally minor, resulting in differences only in localization but not in presence of scintigraphic abnormalities. The second reading resulted in an altered diagnosis in only two cases.

TABLE II

Test Results According to the Degree of Coronary Arterial Involvement in 41 Patients With Significant Lesions

Vessels Involved (no.)	Patients (no.)	Stress Electrocardiogram		Positive Scintigram
		Positive	Equivocal	
1	8	1	4	6
2	18	10	4	16
3	15	7	6	13
Totals	41	18	14	35

Discussion

Methods of diagnosing coronary disease: The standard for diagnosis of coronary artery disease remains the indirect anatomic evidence of selective coronary angiography. In a rough, imprecise manner, the degree of coronary stenosis is assessed and assumptions are made concerning its effect on myocardial blood supply and its pathologic significance. No effort is made to evaluate objectively myocardial demands. The stress electrocardiogram attempts to assess in a noninvasive manner both components of the oxygen supply/demand ratio. Presumably this test is abnormal when a decrease in this ratio reaches pathologic significance regardless of the observed coronary arterial anatomy. Potentially this eliminates our need to quantitate visually the coronary lesion involved. However, stress electrocardiography has problems of insensitivity and nonspecificity.[16,17] A variety of conditions, including conduction defects, left ventricular hypertrophy, drugs, hyperventilation and electrolyte abnormalities, make interpretation of the stress electrocardiogram hazardous.[18–21] Even the female sex has been invoked as a potential cause of the false positive stress test.[22]

Relative myocardial perfusion scintigraphy using thallium-201 is another noninvasive method of diagnosing pathologically significant coronary lesions without direct anatomic assessment. As an indicator of relative myocardial perfusion, scintigraphy evaluates coronary supply and identifies the heterogeneity of myocardial blood flow evoked by increasing coronary flow demand in vessels with varied and limited abilities to accommodate this demand and having an altered "coronary flow reserve."[23] Although flow through stenotic vessels may be normal at rest, exercise stimulates a less than normal increment in the flow through vessels with a diminished flow reserve.[23] The results of such altered reserve among normal, partially stenotic and occluded vessels is stress-induced heterogeneity of coronary flow, appreciated in the scintigram as "hot and cold" regions.

Advantages of scintigraphy: The anatomic correlation between thallium-201 scintigraphic defects and lesions on angiography was excellent in our study and in general agreement with the findings of Bailey et al.[24] Such localization of coronary lesions is not possible with single lead electrocardiographic monitoring systems and would probably present difficulties for multiple lead systems.[2,3,25] The ability of relative perfusion scintigraphy to identify multiple lesions in a given patient has not previously been reported. Although scintigraphy quite sensitively identified patients with coronary lesions, it identified only 46 percent of all involved vessels. In the presence of an adjacent scintigraphic defect, the image could not exclude a coronary lesion in an apparently normally perfused region. In patients with isoelectric S-T segments at rest, perfusion scintigraphy is more accurate and probably more sensitive and specific than stress electrocardiography for the identification of coronary disease. Even in patients with depressed S-T segments at rest, scintigraphy was probably more specific and certainly more accurate than stress electrocardiography. Four patients with significant coronary lesions had a normal stress electrocardiogram and an abnormal stress scintigram at suboptimal stress, thus indicating another level where the stress scintigram has greater sensitivity than the stress electrocardiogram. The presence of both an abnormal stress electrocardiogram and an abnormal stress scintigram guaranteed the presence of significant coronary disease in our study. These findings agree with and extend our observations and those of others in studies using rubidium-81[2,3] as well as the preliminary data from studies using thallium-201.[26,27] However, although others have shown that scintigraphy adds to the diagnostic sensitivity of stress electrocardiography, increased accuracy of scintigraphy alone has not previously been documented and Bailey et al.[24] could only approximate image specificity because most of their "normal" subjects did not undergo cardiac catheterization. We have shown that scintigraphic evaluation maintains its accuracy even in the setting of S-T segment depression at rest, a condition that often is related to sensitive but nonspecific results and that may prevent or cloud stress test interpretation in as many as one fourth to one third of patients with potential coronary artery disease.[28,29] This finding

supports the preliminary results of Bailey et al.[24] in patients with equivocal treadmill results. However, whereas they noted that scintigraphy improved sensitivity for coronary diagnosis in such patients, our study indicates that it improved specificity. Similar to our experience with the stress scintigram and similar to the results of others,[30] we found that scintigrams obtained at rest were extremely sensitive for identifying and localizing prior transmural infarction in the few cases studied.

We monitored only a single electrocardiographic lead. Although it has been shown that monitoring inferior as well as anterior leads may increase the sensitivity of the electrocardiographic technique, it would probably also decrease the specificity and probably would not help to resolve the equivocal test.

Clinical implications: Our standard for the diagnosis of coronary artery disease was based on assessment of coronary angiographic results. Although scintigraphic correlation with angiographic data was clear, the true indicator of significant disease remains unclear. Cases of false positive or false negative scintigrams may in part reflect only our difficulty in assessing the anatomic degree and significance of coronary stenosis. In fact, three patients with "significant" lesions on angiography had normal findings on stress electrocardiography and scintigraphy. Alternatively, the latter two methods may be insensitive to subtle ischemic changes. Similarly, the exact meaning of the abnormal stress electrocardiogram in the absence of significant coronary lesions remains unclear. It is likely that scintigraphic and electrocardiographic indicators of myocardial ischemia measure different variables. The stress-induced scintigraphic abnormalities largely reflect perfusion changes,[3–9,11,25,26,30] whereas stress-induced electrocardiographic changes probably reflect hypoxic, metabolic and electrophysiologic alterations resulting from changes in perfusion. Metabolic evidence of ischemia due to small vessel coronary disease or other cause was not available. However, other possible causes of myocardial ischemia do not carry the dire prognosis of significant large vessel coronary disease.[31] Scintigraphy is more accurate than stress electrocardiography in diagnosing large vessel coronary disease. This increased accuracy of perfusion scintigraphy is probably the reason for its success thus far in differentiating coronary artery disease from other noncoronary causes of ischemia.[32,33] More definite assessment and resolution of these problems may occur with combined angiographic, scintigraphic and metabolic studies.

Initial fears of the inability of the scintigraphic method to identify the presence of severe triple vessel disease due to generalized and uniform diminution of coronary flow reserve appear unrealized. Whereas Bailey et al.[24] found increased scintigraphic sensitivity with increased arterial involvement, we found that the scintigram was equally sensitive in single, double or triple vessel disease. However, the stress electrocardiogram showed a tendency toward increased sensitivity with increased arterial involvement, as previously documented.[23,34] We studied only two patients with left bundle branch block, both with a correct scintigraphic diagnosis, and can make no specific conclusion concerning recent observations[35] on resting membrane abnormalities and their scintigraphic effects in this condition.

Perfusion scintigraphy did not identify all involved coronary vessels. Using the technique as an indicator of relative coronary flow, one would expect the region of greatest flow to appear most intense. Regions of normal flow could not be differentiated from regions of absolutely reduced yet "best" flow in a patient with multivessel disease. The regions best visualized in the stress scintigrams shown in Figures 6 and 8, both from patients with triple vessel disease, were perfused by severely stenotic vessels. Indirect evidence that the region of greatest image intensity is indeed best perfused may come from future evaluation of the coronary collateral circulation. Similarly, regions perfused by significantly stenotic vessels may appear normally or "best" perfused if they are in proximity to more severely stenotic lesions or regions of dense infarction.[3] This may explain the single patient with prior infarction and significant coronary disease who had a positive stress electrocardiogram in the absence of stress-induced image abnormalities.

Technical considerations: Perfusion scintigraphy with thallium-201 is simple to perform, safe and reproducible.[3,27] The 73 hour thallium-201 physical half-life permits a storage shelf life of 1 week, and imaging is facilitated by the radionuclide's small energy of emission (70 to 80 kev) compared with the larger emission energy of agents such as potassium-43 and rubidium-81. However, a potential hazard of the smaller energy of emission of thallium-201 is that tissue attenuation may hamper myocardial resolution, especially in the resting image and in the obese patient where target to background ratios are lowest. Probably because of image attenuation, the myocardium was most poorly resolved in the left lateral projection. Scintigraphic defects seen only in this projection were not interpreted as abnormal unless associated with defects in other projections. We encourage use of the highest resolution scintillation camera. The prolonged half-life of thallium-201 may hamper rapid performance of repeat studies and the radionuclide's present high cost is another disadvantage. Although computer methods of enhancing images may aid scintigraphic interpretation, there is as yet no such established method that improves sensitivity without increasing the false positive rate. Although Bailey et al.[24] demonstrated good scintigraphic results using processed images, such findings have little relevance to centers seeking to apply the study clinically without computer assistance. Our study demonstrated excellent results without computer enhancement.

Acknowledgment

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Hemodynamics at Rest and During Supine and Sitting Bicycle Exercise in Normal Subjects

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To assess left ventricular function and to compare mean pulmonary wedge pressure and left ventricular end-diastolic pressure in the supine and sitting positions, 10 patients without demonstrable cardiovascular disease underwent hemodynamic studies at rest and during exercise in the two positions. At rest the values for heart rate were higher and the values for cardiac index, stroke index, left ventricular stroke work index, mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure were lower in the sitting position. During both supine and sitting exercise left ventricular end-diastolic pressure, cardiac index, stroke index and left ventricular stroke work index increased significantly from the resting values. Comparison of data during exercise revealed higher values for heart rate and rate-pressure product and lower values for pulmonary capillary wedge pressure, left ventricular end-diastolic pressure and stroke index in the sitting position; systolic and mean systemic pressure, cardiac index and left ventricular stroke work index were similar during the two exercise periods. When absolute changes from rest to exercise were compared, the increase in heart rate, systolic blood pressure, pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, cardiac index, stroke index, and left ventricular stroke work index were similar in the two positions. There was a good correlation between left ventricular end-diastolic pressure and pulmonary capillary wedge pressure at rest and during exercise in the two postures.

Recent studies in patients with coronary artery disease[1] have shown marked differences in the hemodynamic patterns in the supine and upright positions both at rest and during exercise. In these patients, left ventricular filling pressures were substantially lower during upright exercise than during exercise in the supine position. Comparative hemodynamic data are available in normal subjects at rest and during exercise in supine and upright postures,[2–13] and the normal values for left ventricular filling pressure during supine exercise have been defined.[14,15] However, no information is available regarding left ventricular filling pressure either at rest or during exercise in the upright posture.

This communication presents hemodynamic data including left ventricular end-diastolic pressure and pulmonary capillary wedge pressure measurements obtained at rest and during supine and upright exercise in patients without demonstrable cardiovascular disease.

Methods

Subjects: Hemodynamic investigations with subsequent selective coronary cinearteriography and left ventriculography were performed in 10 men aged 32 to 58 years (average 46 years). All were leading a sedentary life and were referred for investigation of chest pain. The majority of of these patients had been considered to be suffering from coronary artery disease and had been advised by their family physicians to restrict their level of activity. All had sinus rhythm and were normotensive. Cardiac examination was normal and no subject had

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clinical or radiologic evidence of cardiomegaly or cardiac failure. None manifested chest pain or S-T segment depression during treadmill exercise testing. Despite the atypical nature of symptoms in many patients and the negative stress test it was felt advisable to perform angiographic studies to determine whether coronary artery disease was present. None had been taking medications for at least 7 days before the investigation.

Protocol: On the day before the investigation, the patients were taken to the laboratory, the study explained and informed consent obtained. Each patient then exercised on a bicycle ergometer in both the supine and sitting positions. During the supine exercise, the ergometer was positioned over the catheterization table, the axle being 12 inches (30.5 cm) above the table level. The work load that would induce mild fatigue while permitting exercise to be continued for 4 to 6 minutes was determined for each subject. These work loads (range 300 to 1250 kilopond-meters per minute) were recorded and were subsequently utilized in the definitive studies.

Patients were studied in the fasting state 2 hours after receiving an oral dose of 10 mg of diazepam. Under local anesthesia, the brachial artery and a vein were isolated in the right antecubital fossa. A no. 7 Swan-Ganz catheter was passed to one of the branches of the pulmonary artery supplying the right lower lobe. The position of the catheter was considered satisfactory only if good quality pulmonary capillary wedge pressure measurements were obtained after balloon inflation. A no. 8 Lehman ventriculographic catheter was inserted into the left ventricle from the right brachial artery, and the left brachial artery was cannulated with a Teflon® needle using the Seldinger technique.

Each patient was studied in both the supine and sitting positions at rest and during bicycle exercise at the predetermined work loads. A rest period of 15 minutes followed the instrumentation and a 30 minute rest period was interspaced between the two periods of exercise. The order of exercise was randomized; five patients exercised first in the upright position and five patients first in the supine position. Great care was taken in moving patients from the supine to sitting positions with continuous electrocardiographic and left ventricular pressure monitoring.

The electrocardiogram (modified lead V_5) and intracardiac and intravascular pressures were recorded at 5 minute intervals during a 10 minute control period at rest in both the supine and sitting postures, and during the final 2 minutes cardiac output was measured in duplicate with the dye-dilution technique using indocyanine green. During exercise, the electrocardiogram and pressures were monitored continually and recorded at 1 minute intervals. Cardiac output was measured in duplicate between 3 and 5 minutes of exercise and then the final pressure measurements were made and exercise discontinued.

Measurements and recordings: Pressures were measured with P23 DB Statham strain gauges from a zero reference level 5 cm below the level of the angle of Louis in the studies in the supine position, and from the fourth intercostal space at the sternal border in the sitting position. Pressures were measured over at least two respiratory cycles, and the mean pressures in the brachial artery, pulmonary artery and pulmonary capillary wedge positions were obtained electronically. Recordings were made on a photographic recorder at a paper speed of 25 mm/sec; however, for determination of left ventricular end-diastolic pressure and pulmonary capillary wedge pressure, a speed of 100 mm/sec was employed and these pressures were measured at a high level of sensitivity.

Left ventricular stroke work index (g-m/m^2) was calculated using the formula LVSWI = SI × (BAm − LVEDP) × 13.6/1000, where SI = stroke index (ml/beat per m^2), BAm = brachial arterial mean pressure (mm Hg) and LVEDP = left ventricular end-diastolic pressure (mm Hg). *Systolic ejection rate index* (ml/sec per m^2) was calculated using the formula SI/SEP where SEP = systolic ejection period in seconds obtained from the brachial arterial tracings at a speed of 100 mm/sec. In two patients, left ventricular end-diastolic pressure was not measured in the sitting position because of ventricular irritability, and in these patients values of pulmonary capillary wedge pressure were substituted for left ventricular end-diastolic pressure in the calculations for both the supine and sitting position. *The rate-pressure product* (mm Hg/min × 10^{-2}) was calculated as the product of systolic arterial pressure and heart rate × 10^{-2}. The first derivative of the left ventricular pressure curve (dP/dt [mm Hg/sec]) was obtained using an electronic differentiator.

After completion of these hemodynamic studies, selective

TABLE I

Summary of Hemodynamic Data and Statistical Analysis (mean ± standard error of the mean)

	State				*P* Values			
	1. Supine Rest	2. Supine Exercise	3. Sitting Rest	4. Sitting Exercise	1 vs. 2	3 vs. 4	1 vs. 3	2 vs. 4
HR	73 ± 4	128 ± 6	84 ± 4	146 ± 7	<0.001	<0.001	<0.001	<0.005
Pressures (mm Hg)								
Brachial artery								
Systolic	130 ± 5	178 ± 6	132 ± 5	184 ± 7	<0.001	<0.001	NS	NS
Diastolic	76 ± 3	84 ± 3	82 ± 3	89 ± 4	<0.05	<0.05	<0.05	NS
Mean	96 ± 3	119 ± 4	99 ± 4	121 ± 5	<0.001	<0.001	NS	NS
PA	13 ± 1	24 ± 2	13 ± 1	22 ± 1	<0.001	<0.001	NS	NS
PCW	6 ± 1	13 ± 1	4 ± 1	8 ± 1	<0.001	<0.001	<0.001	<0.001
LVED	8 ± 1	16 ± 2	4 ± 1	11 ± 1	<0.001	<0.001	<0.005	<0.001
CI	3.5 ± 0.3	7.7 ± 0.5	2.8 ± 0.2	7.3 ± 0.5	<0.001	<0.001	<0.005	NS
SI	50 ± 5	61 ± 6	35 ± 3	52 ± 5	<0.01	<0.001	<0.001	<0.05
SERI	161 ± 14	227 ± 16	134 ± 9	228 ± 18	<0.001	<0.001	<0.01	NS
LVSWI	61 ± 6	87 ± 6	44 ± 3	80 ± 7	<0.001	<0.001	<0.05	NS
HR × SBP	94 ± 6	228 ± 15	111 ± 8	264 ± 21	<0.001	<0.001	<0.05	<0.05
dP/dt	1601 ± 125	3278 ± 215	1658 ± 188	3777 ± 210	<0.001	<0.001	NS	NS

CI = cardiac index (liters/min per m^2); dP/dt = first derivative of left ventricular pressure (mm Hg/sec); HR = heart rate (beats/min); HR × SBP = rate pressure product (heart rate × systolic blood pressure (mm Hg/min × 10^{-2}); LVED = left ventricular end-diastolic; LVSWI = left ventricular stroke work index (g-m/beat per m^2); NS = not significant; *P* = probability; PA = mean pulmonary arterial; PCW = pulmonary capillary wedge; SERI = systolic ejection rate index (ml/sec per m^2); SI = stroke index (ml/beat per m^2).

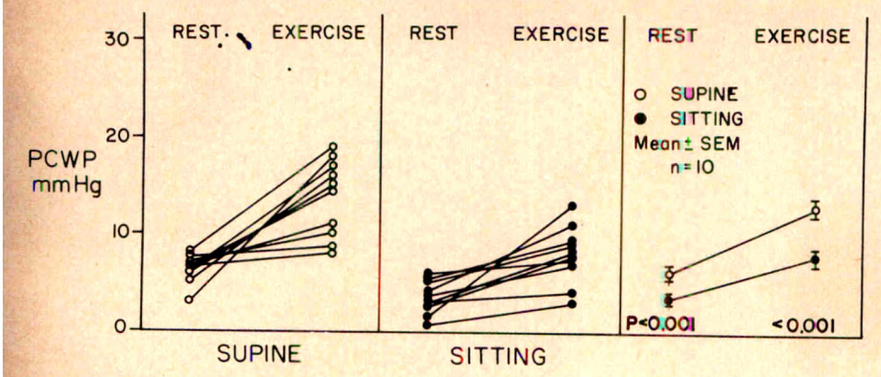

FIGURE 1. Individual and group mean values for mean pulmonary capillary wedge pressure (PCWP) in the supine and sitting positions at rest and during exercise. n = number of subjects; P = probability; SEM = standard error of the mean.

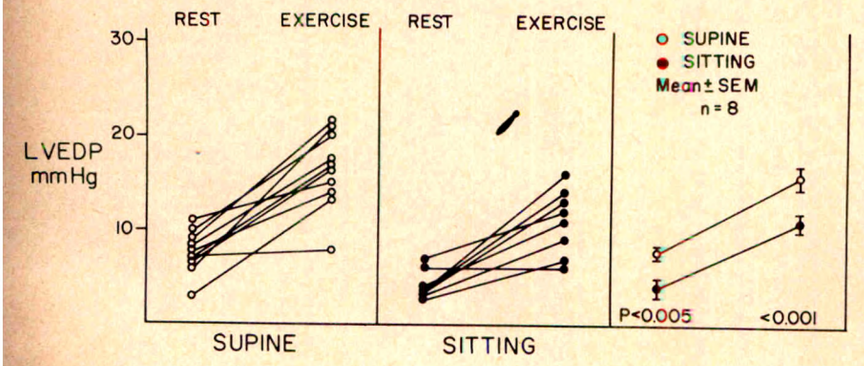

FIGURE 2. Individual and group mean values of left ventricular end-diastolic pressure (LVEDP) in the supine and sitting positions at rest and during exercise. Left ventricular end-diastolic pressure in the sitting position was recorded in only eight subjects.

coronary cineangiography and left ventriculography were carried out in all patients. For the statistical analysis of data, Student's paired t test was used.

Results

The hemodynamic and angiographic studies were completed without complications. None of the patients experienced chest pain or manifested S-T segment depression during exercise. Two subjects performed greater work loads in the sitting position and another performed a greater work load in the supine position. The remaining seven subjects performed similar work loads during the two exercise periods. The work loads required to induce fatigue during upright exercise (590 ± 289 kilopond-meters per minute) (mean ± standard deviation) and during supine exercise (589 ± 211 kilopond-meters per minute) were similar. Left ventriculography and selective coronary angiography revealed normal findings in all subjects.

Studies in the Supine Position (Table I)

Resting hemodynamics: In the supine studies, mean pulmonary capillary wedge pressure averaged 6 mm Hg (range 3 to 8), and left ventricular end-diastolic pressure averaged 8 mm Hg (range 4 to 11) (Fig. 1 and 2). These differences were significant ($P < 0.01$) and the correlation coefficient was $r = 0.94$ (Fig. 3). Cardiac index averaged 3.5 liters/min per m^2 (range 3.0 to 5.0), stroke index averaged 50 ml/m^2 (range 32 to 84) and left ventricular stroke work index averaged 61 $g\text{-}m/m^2$ (range 47 to 108).

Exercise hemodynamics: During exercise there were significant increases from resting values in heart rate; systolic, diastolic and mean systemic arterial pressure; rate-pressure product; mean pulmonary arterial pressure and pulmonary capillary wedge and left ventricular end-diastolic pressures (Fig. 1, 2, 4 and 5). The group mean values were heart rate 128 ± 6 beats/min (mean ± standard error of the mean), systolic blood pressure 178 ± 6 mm Hg and mean pulmonary arterial pressure 24 ± 2 mm Hg. The mean pulmonary capillary wedge pressure, 13 ± 1 mm Hg, was less than the left ventricular end-diastolic pressure, 16 ± 2 mm Hg ($P < 0.01$); the correlation coefficient between the two pressures was $r = 0.96$ (Fig. 3). During exercise, increases in cardiac index, stroke index, left ventricular stroke work index and systolic ejection rate index were observed in all subjects (Fig. 6 to 8).

Studies in the Sitting Position (Table I)

Resting hemodynamics: In the sitting position, mean pulmonary capillary wedge pressure averaged 4 mm Hg (range 1 to 6) and left ventricular end-diastolic pressure, recorded in eight patients, averaged 4 mm Hg (range 3 to 7); the correlation coefficient between the

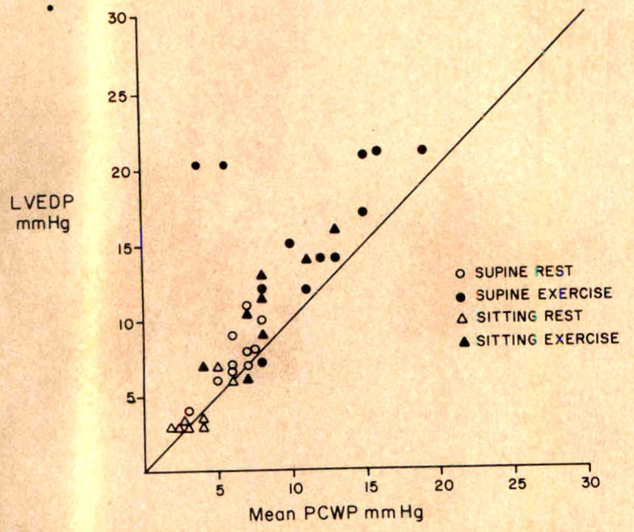

FIGURE 3. Relation between mean pulmonary capillary wedge pressure (PCWP) and left ventricular end-diastolic pressure (LVEDP) at rest and during exercise. There is a good correlation between the two pressures at rest ($r = 0.94$ supine and 0.92 sitting) and during exercise ($r = 0.96$ supine and 0.91 sitting).

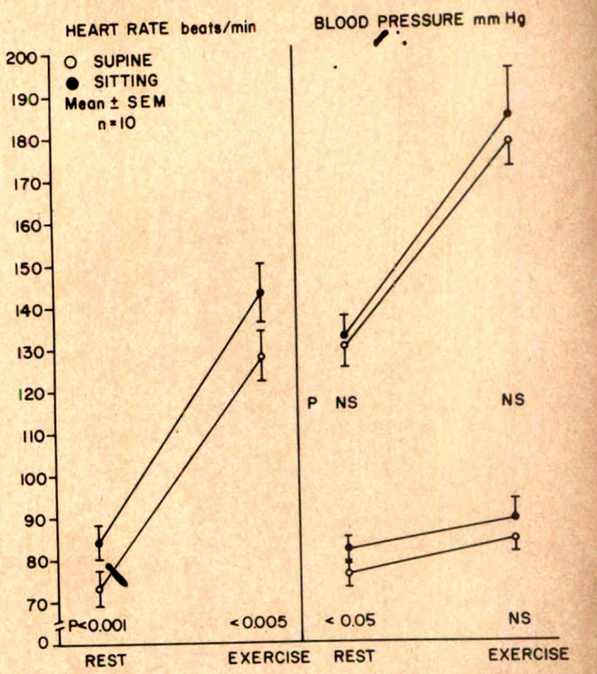

FIGURE 4. Group mean values for heart rate and systemic arterial blood pressure at rest and during exercise. NS = not significant.

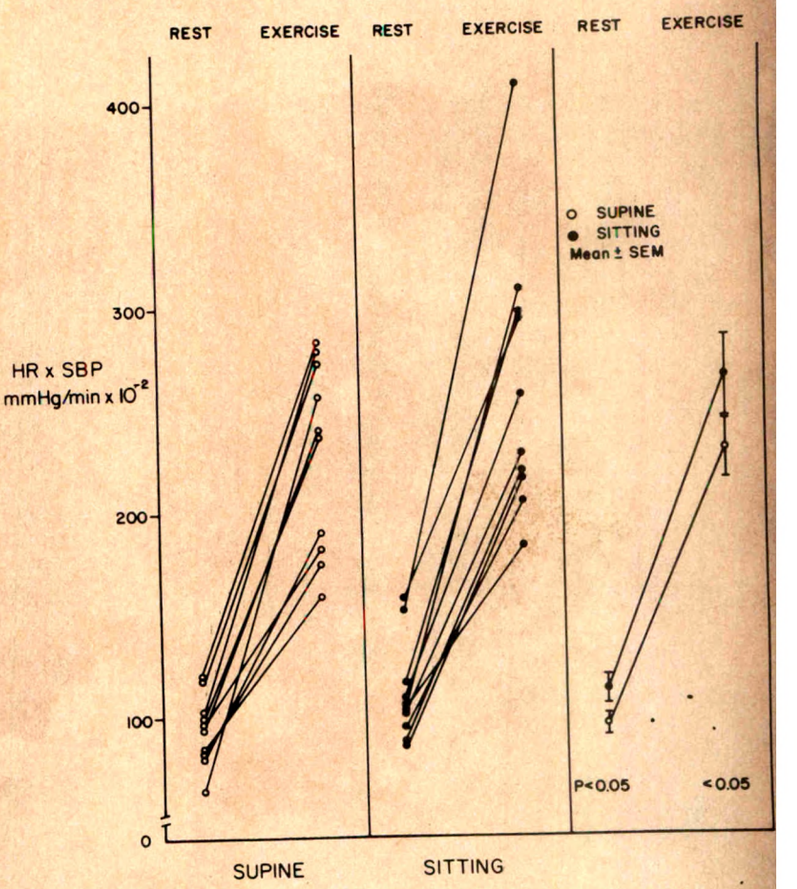

FIGURE 5. Individual and group mean changes in rate-pressure product from rest to exercise. Both at rest and during exercise, group mean values of rate-pressure product were significantly higher in the sitting position. HR × SBP = rate-pressure product (heart rate × systolic blood pressure [mm Hg/min × 10^{-2}]).

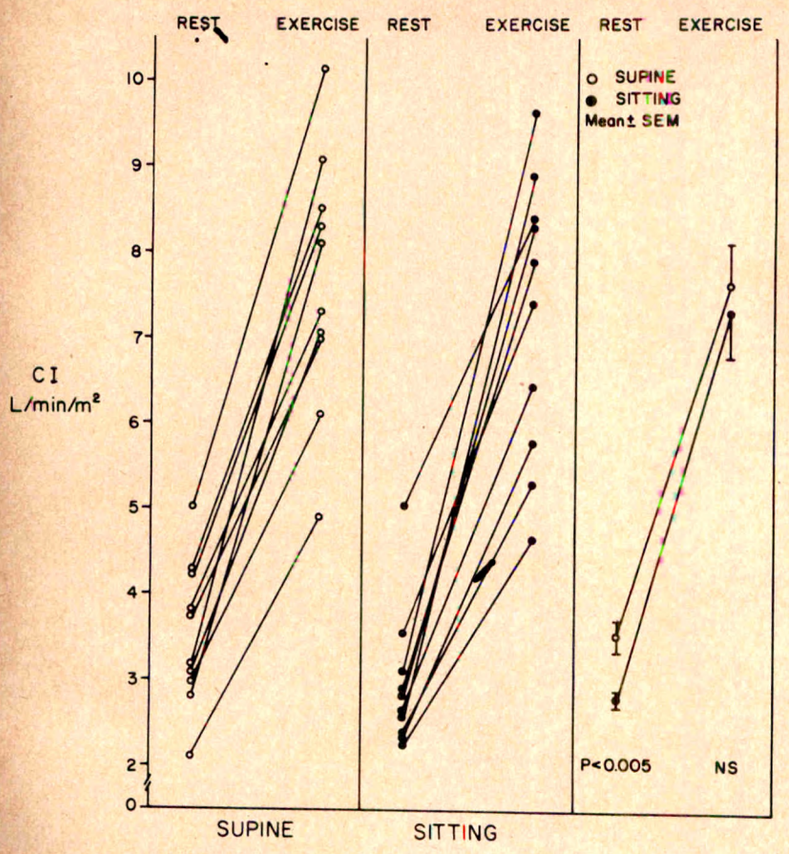

FIGURE 6. Individual and group mean values for cardiac index (CI) at rest and during exericse. At rest, cardiac index is significantly lower in the sitting position.

two pressures was $r = 0.92$ (Fig. 3). The cardiac index averaged 2.8 liters/min per m^2 (range 2.4 to 3.7), stroke index averaged 35 ml/m^2 (range 24 to 52) and left ventricular stroke work index averaged 44 g-m/m^2 (range 32 to 57).

In comparison with the resting values in the supine position, the values for heart rate and diastolic arterial pressure were higher and those for mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure were lower in the sitting posture (Fig. 1, 2 and 4). In the sitting position, mean cardiac index was 2.8 ± 0.2 liters/min per m^2 and was significantly lower than in the supine position (3.5 ± 0.3 liters/min per m^2) ($P < 0.001$) (Fig. 6). Similarly, stroke index (35 ± 3 versus 50 ± 5 ml/beat per m^2) ($P < 0.001$) and left ventricular stroke work index (44 ± 3 versus 61 ± 6 g-m/beat per m^2) ($P < 0.001$) were lower in the sitting position (Fig. 7 and 8).

Exercise hemodynamics: During exercise in the sitting position, there were increases in heart rate, systolic and mean systemic arterial pressures, mean pulmonary arterial pressure and pulmonary capillary wedge and left ventricular end-diastolic pressures (Fig. 1, 2, 4 and 5). The mean values were heart rate 146 ± 7 beats/min, systolic blood pressure 184 ± 7 mm Hg, mean pulmonary arterial pressure 22 ± 1 mm Hg, mean pulmonary capillary wedge pressure 8 ± 1 mm Hg and left ventricular end-diastolic pressure 11 ± 1 mm Hg. There was a tendency for left ventricular end-diastolic pressure to be greater than the mean pulmonary capillary wedge pressure ($P < 0.05$); the correlation coefficient between the two pressures was $r = 0.91$ (Fig. 3). During exercise, increases in cardiac index, stroke index, left ventricular stroke work index and systolic ejection rate index were observed in all subjects (Fig. 6 to 8).

Comparison of values obtained during supine exercise showed that in the sitting position there were significantly higher values for heart rate and rate pressure product (Fig. 4 and 5), similar values for systolic and mean systemic arterial pressures, mean pulmonary arterial pressure, cardiac index, left ventricular stroke work index and systolic ejection rate index (Fig. 4, 6 and 8) and lower values for mean pulmonary capillary wedge pressure, left ventricular end-diastolic pressure and stroke index (Fig. 1, 2 and 7).

However, when changes from rest to exercise in the sitting and supine postures were compared, it was observed that the increases in the variables measured were similar in the two positions: heart rate (59 versus 55 beats/min), systolic blood pressure (52 versus 47 mm Hg), mean systemic arterial pressure (22 versus 23 mm Hg), rate-pressure product (145 versus 134 mm Hg/min $\times 10^{-2}$), mean pulmonary arterial pressure (9 versus 11 mm Hg), mean pulmonary capillary wedge pressure (4 versus 7 mm Hg), left ventricular end-diastolic pressure (7 versus 8 mm Hg), cardiac index (4.5 versus 4.2 liters/min per m^2), stroke index (17 versus 11 ml/beat per m^2) and left ventricular stroke work index (36 versus 26 g-m/beat per m^2). On the other hand, increases in systolic ejection rate index were greater in the sitting position than during supine exercise (94 versus 66 ml/sec per m^2) ($P < 0.05$).

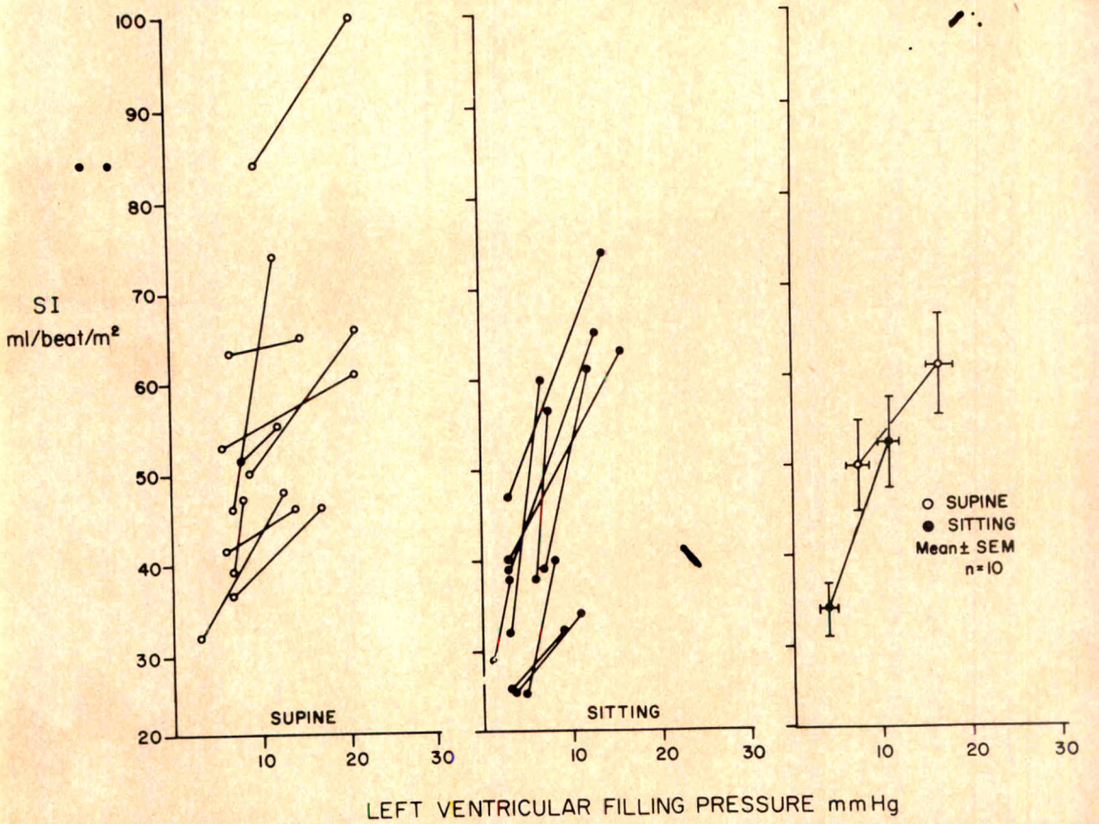

FIGURE 7. Relation between left ventricular filling pressure and stroke index (SI) at rest and during exercise in the two positions. The lines joining the points in the left and middle columns represent individual values at rest and during exercise, respectively. The group mean values for stroke index and left ventricular filling pressure were significantly lower both at rest and during exercise in the sitting position.

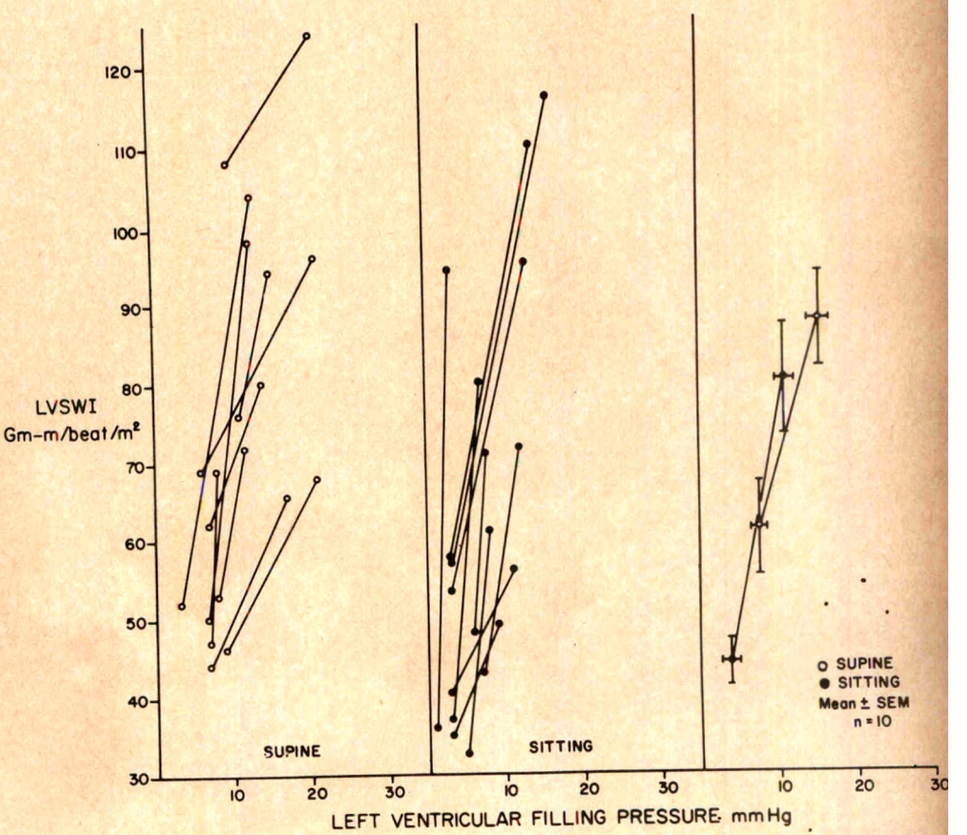

FIGURE 8. Relation between left ventricular filling pressure and left ventricular stroke work index (LVSWI) (g-m/beat per m^2) at rest and during exercise in the two positions. The lines joining the points in the left and middle columns represent individual values at rest and during exercise, respectively. At rest, the group mean values for left ventricular stroke index and left ventricular end-diastolic pressure were significantly lower in the sitting position. However, during exercise, the group values for left ventricular stroke index were similar in the two postures.

Discussion

Hemodynamics at Rest in Supine Versus Sitting Posture

This study has shown that in normal untrained subjects, the hemodynamic profile in the supine and sitting postures is different both at rest and during exercise. At rest in the supine position the left ventricular filling pressure was normal in all subjects. In normal subjects, no information is available regarding left ventricular end-diastolic pressure or pulmonary capillary wedge pressure in the upright position. Mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure averaged 4 mm Hg in the upright posture; these values were significantly lower than those obtained in the supine posture. It should be pointed out that the zero reference levels for pressure measurement were different in the two positions. The standard technique for measuring pressures in the supine position in our laboratory is from a zero reference level 5 cm below the level of the angle of Louis, whereas for studies in the sitting position we chose a reference level at the fourth intercostal space at the border of the sternum. In the sitting position, it was not possible to define exactly the location of the catheter in the ventricular chamber. The mid portion of the left ventricle in the sitting posture often lies in the fifth or sixth intercostal space and it is possible that the pressures recorded from this chamber in the sitting position were somewhat underestimated.

The resting values for cardiac index, stroke index and left ventricular stroke work index were significantly lower in the sitting position and these observations are in keeping with previous reports in normal human subjects and in patients with coronary artery disease.[1–13] In the present study, the heart rate in the sitting position was higher than in the supine posture and it would appear that the lower cardiac index and stroke index in this position were due primarily to diminished venous return.

Hemodynamics During Exercise in Supine Versus Sitting Posture

Left ventricular pressure: During supine exercise, both the mean pulmonary capillary wedge pressure and left ventricular end-diastolic pressure increased significantly. The increase in left ventricular filling pressure during supine leg exercise observed in our study and in previous reports[14,15] is at variance with some published data in normal subjects.[16–18] In the latter reports, left ventricular filling pressure and volumes during supine exercise either did not change or actually decreased from the resting values. These differences may well be due to varying methods of carrying out exercise in the supine posture. In our studies, the bicycle ergometer was placed so that the legs were elevated above the chest during supine exercise. Thus, increased venous return might have been responsible for the increased left ventricular filling pressures. This seems unlikely, however, because the left ventricular end-diastolic pressure in the same patient increased by a similar amount during upright bicycle exercise.

There are no previous data relating to left ventricular end-diastolic pressure or pulmonary capillary wedge pressure during exercise in the sitting position in normal subjects. In our study during exercise in the sitting position, both the mean pulmonary capillary wedge and left ventricular end-diastolic pressures increased. Although the absolute values for these pressures during exercise were lower in the sitting than in the supine posture, the increases in these pressures from rest to exercise in the two postures were similar. In contrast, previous studies in patients with coronary artery disease[1] demonstrated significantly smaller increases in left ventricular filling pressure during sitting than during supine bicycle exercise.

Cardiac output: In normal human subjects, the cardiac output during supine leg exercise increases as a linear function of oxygen consumption.[11] However, the changes reported in stroke volume during exercise have been variable. A review of published findings by Rushmer[19] in 1959 showed that in normal subjects the stroke volume changed only slightly over a wide range of exercise. Ten healthy men studied by Bevegård et al.[5] more than doubled their cardiac output during supine leg exercise with increases in stroke volume averaging less than 5 percent. Ross and co-workers[18] studied patients with no evidence of impaired cardiac reserve. During supine exercise, these subjects attained a cardiac index of up to 10 liters/min per m^2, whereas the stroke volume was unchanged in four and increased in two subjects and decreased in one subject. In our study, cardiac output during supine leg exercise increased significantly in all subjects; stroke volume increased in nine and was unchanged in the remaining subject. Cardiac output increased an average of 120 percent during supine exercise and stroke volume an average of 22 percent. These observations are in agreement with previous reports in normal subjects from this laboratory.[14] Thus, it would appear that in normal subjects there is a wide individual variation in the changes in stroke volume during supine leg exercise. It is difficult to reconcile the differences in results from different laboratories, but these may well be due to differences in the study population or the leg position during exercise. In our study, an increase in left ventricular stroke work index was observed during supine exercise in all subjects. These observations are in accord with previous reports in normal subjects,[14] but are different from those reported in patients with coronary artery disease.[1,14] In the latter group, the cardiac index increased but there was no significant increase in stroke index or left ventricular stroke work index during exercise in the supine posture.[1,14]

During exercise performed in the sitting position, the cardiac output also increases linearly with oxygen consumption.[11] In our study, the cardiac output during bicycle exercise in the sitting position increased by 160 percent from the resting values in this position. However, the values obtained during supine and sitting exercise were similar despite significantly lower resting values in the sitting position.

Stroke volume: When a person sits or stands, the stroke volume and heart volume consistently dimin-

ish.[4,20,21] Beginning at this lower baseline, the stroke volume increases promptly at smaller work loads and approaches the values obtained during supine rest.[4,6,7,22–24] In our study, during exercise in the sitting position, stroke index increased by 71 percent from the resting values in this posture. However, this value during upright exercise was similar to the resting stroke index in the supine posture but was significantly lower than the stroke index during exercise in the supine posture. Left ventricular stroke work index during sitting bicycle exercise increased in all subjects and both the absolute values of this variable during supine and sitting exercise and the increase from rest to exercise were similar in the two postures.

Pulmonary capillary wedge pressure as an index of left ventricular diastolic pressure: Numerous studies in the supine position have confirmed that in the absence of severe pulmonary hypertension or obstruction at the level of the pulmonary veins or left atrium, the mean pulmonary capillary wedge pressure corresponds approximately to the left atrial pressure, which itself is approximately equal to the diastolic pressure in the left ventricle.[1,25,26] Our study shows that the wedge pressure provides a good index of left ventricular end-diastolic pressure at rest and during exercise in both the supine and upright postures. Thus, it should be possible to explore left ventricular hemodynamics in the upright posture using the flotation catheter technique, which is safer than obtaining direct left ventricular pressures.

Acknowledgment

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Abnormal Platelet Survival Time in Men With Myocardial Infarction and Normal Coronary Arteriogram

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Platelet survival time was measured in eight men who had an acute transmural myocardial infarction and were subsequently found to have a normal coronary arteriogram. Platelet survival (chromium-51 labeling) was shortened in all men (2.4 ± 0.11 days; average half-time ± standard error of the mean) and different from that in eight age-matched normal men (3.7 ± 0.08 days) ($P < 0.001$). Three patients had recurrent venous thromboembolism and one had had iliofemoral arterial thromboembolism. Platelet survival was shortened (2.9 ± 0.12 days) in 11 of 16 age-matched men with transmural infarction who had arteriographic evidence of coronary obstructive disease. These results suggest that platelet survival time is shortened in patients with infarction who subsequently are shown to have a normal coronary arteriogram and that arterial thrombosis may be responsible for the infarction.

Although myocardial infarction is usually associated with arteriographic evidence of atherosclerotic coronary obstruction, examples of infarction in the absence of coronary artery disease have been reported.[1–10] Arterial thrombosis, small vessel coronary disease and arterial spasm are several possibilities that have been considered in the pathogenesis of this problem.[11] A few patients have been described who had thromboembolic occlusion and myocardial infarction at the time of cardiac catheterization.[3,12,13] Coronary arteriograms obtained several months after the infarction were normal, suggesting that complete resolution of thromboembolic coronary arterial occlusion can occur.

In this study platelet survival time was measured in eight men with a transmural myocardial infarction who subsequently were found to have a normal coronary arteriogram. Platelet survival time was also measured in eight age-matched men with a normal arteriogram who had had no infarction and in 16 men with a history of infarction and arteriographic evidence of coronary obstructive disease.

Material and Methods

Patients: Eight men with a myocardial infarction and a normal coronary arteriogram were studied. All had sustained an acute transmural infarction (new Q waves in at least three electrocardiographic leads with evolving S-T changes) 6 to 20 months before study. These men included all patients that we recognized to have this clinical entity. To qualify for study a patient was required to have electrocardiographic evidence for evolving transmural infarction and to have had subsequent coronary arteriography. In addition, all the men had impaired wall motion of the infarcted segment demonstrated with cineventriculography. Six had an anterior wall infarction and two an inferior wall infarction (Table I). Three men had a history of recurrent venous thrombosis and were started on anticoagulant therapy at the time of their infarction. One other patient had a sudden occlusion of the right common femoral artery 5 months before sustaining an acute infarction; embolectomy yielded a thrombus, and a subsequent arteriogram was normal. None of these patients had cardiac valve disease.

Platelet survival time was also measured in eight normal men. These men had a normal coronary arteriogram and had not had a myocardial infarction. They

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TABLE I

Men With Infarction and a Normal Coronary Arteriogram

Case no.	Age (yr)	Location of Infarction	Other Thrombosis	Platelet Survival Time (t 1/2) (days)
1	28	Anterior	None	2.6
2	29	Anterior	RVTE*	1.9
3	32	Inferior	RVTE	2.7
4	33	Inferior	Femoral occlusion	2.4
5	34	Anterior	RVTE	2.3
6	38	Anterior	None	2.1
7	40	Anterior	None	2.5
8	42	Anterior	None	2.8
Average ± SEM				2.4 ±0.11

* RVTE = recurrent venous thromboembolism; SEM = standard error of the mean.

were selected from a larger group of normal men by age-matching with the men with infarction. In addition, 16 men in pairs, age-matched with the eight men with infarction, were studied. These 16 men had had a transmural infarction and had arteriographic evidence of coronary obstructive disease.

Platelet survival time: This was measured by labeling the platelets from about 400 ml of the patient's venous blood with 100 to 150 μCi of chromium-51.[14,15] Platelet survival half-time was obtained by computer-assisted least squares fit of a single exponent to 7 days of platelet count-rate data.

Results

Men with myocardial infarction and a normal coronary arteriogram: Platelet survival time was shortened (half-time less than 3.3 days) in all eight men with a myocardial infarction and a normal coronary arteriogram (2.4 ± 0.11 days; average ± standard error of the mean) (Table I). None of these men had hyperlipoproteinemia. Patients 4, 6, 7 and 8 smoked cigarettes (between 1/2 and 2 packs a day) at the time of their infarction and through the measurement of platelet survival time. The coronary arteriogram was normal in all but two men. Patients 4 and 8 had minor luminal irregularities in the right coronary artery and Patient 8 had a minor lesion (less than 20 percent luminal narrowing) in the left anterior descending coronary artery.

Men with a normal coronary arteriogram without infarction: Platelet survival time was normal in all eight of the age-matched normal men and the average was different from that of the men with infarction and a normal arteriogram (3.7 ± 0.08 days) ($P < 0.001$) (Fig. 1). None of the normal men had had thrombosis, none had hyperlipoproteinemia and three smoked cigarettes at the time of study. All underwent coronary arteriography for evaluation of chest pain and the arteriograms were normal in each patient. All had a normal resting 12 lead electrocardiogram. Platelet survival time averaged 3.7 ± 0.04 days in 18 other normal men. Selection of any eight normal men for comparison with the men with infarction would not alter the differences between these two groups. None of the 26 men had a platelet survival time of less than 3.3 days.

Men with myocardial infarction and obstructive coronary disease: Platelet survival time was shortened (2.9 ± 0.12 days) (Fig. 1) in 11 of the 16 men (69 percent) with a history of infarction and abnormal coronary arteries (more than 60 percent obstruction) on arteriography. Average platelet survival time for these 16 men was significantly shorter than in the normal men and significantly longer than in the 8 men with infarction and normal coronary arteriograms. Five of these men had inferior infarction and 11 had anterior, anterolateral or superior-lateral infarction. Nine men had total occlusion of the coronary artery that supplied the infarcted segment and all nine had a shortened platelet survival time. The other seven men had high grade obstructive lesions in the coronary artery to the infarcted segment and five of these had normal platelet survival time.

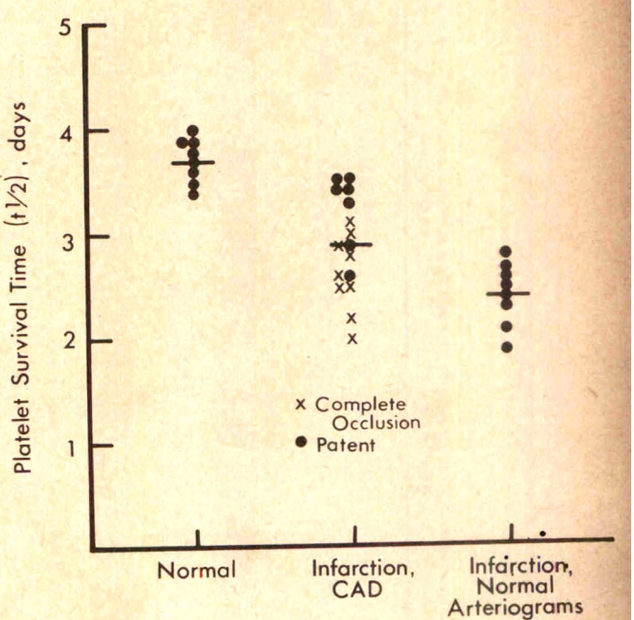

FIGURE 1. Platelet survival time in eight normal men **(left)**, 16 men with a history of myocardial infarction and arteriographic evidence of coronary artery disease (CAD) **(center)**, and eight men with a history of infarction and a normal coronary arteriogram **(right)**. For men with coronary disease, **crosses** represent complete occlusion and **closed circles** represent obstructed but patent coronary arteries.

Discussion

The present study describes eight men who had sustained a transmural myocardial infarction and subsequently were shown to have a normal coronary arteriogram. In all men platelet survival time was shorter than in age-matched control subjects, and this finding suggests that coronary arterial thrombosis occurred and resulted in infarction. Presumably the thrombus had completely recanalized by the time of coronary angiography. Of interest is the finding of recurrent venous thromboembolism in three men and of femoral arterial thromboembolism in one other.

Platelet function and coronary thrombosis: Myocardial infarction has resulted from coronary arterial thromboembolism when this occurred at the time of cardiac catheterization.[3,12,13] Coronary arteriography subsequently undertaken in these patients showed recanalization of the occluded coronary artery. Thus, coronary arterial thrombotic occlusion can recanalize with time. Bruschke et al.[6] described five patients with infarction and a subsequent normal coronary arteriogram. One of these (Case 2) on three occasions underwent coronary arteriography; the films demonstrated first a normal, then an occluded coronary artery and finally restoration of a normal arterial lumen.[6] These reports seem to confirm the idea that coronary thrombosis can cause infarction and that coronary arterial patency can be restored.

Salky and Dugdale[16] studied three patients with infarction and a normal coronary arteriogram and observed shortened platelet survival in all three. One of the young women with infarction and a normal angiogram studied by Glancy et al.[5] and the women described by Ciraulo[10] were taking oral contraceptive agents. Two of the nine patients described by Khan and Haywood[9] were taking amphetamines. Kimbiris et al.[8] observed a platelet count in excess of 600,000 per mm^3 in one of their three cases. Thus, in addition to our patients, a number of patients with infarction and normal arteriograms had abnormalities of platelet reactivity, thrombocytosis or were taking a drug that possibly could have precipitated thrombosis.

Platelet function and atherosclerosis: Shortened platelet survival time was also observed in our patients with coronary arteriosclerotic obstruction and a history of myocardial infarction. Although controversy exists in respect to the contribution of platelets to the pathogenesis of atherosclerosis, platelets play an important role in arterial thrombosis and may be important in the progression of existing lesions and the complications of atherosclerosis.[17,18] It is interesting that platelet survival time was shortened in all of our patients with complete occlusion of the coronary artery to the infarcted segment.

Perhaps our patients with infarction and normal arteriograms represent one end of a continuum in which thrombosis has occurred on a minimally abnormal arterial surface. These patients all have shortened platelet survival time. The other end of the continuum would include patients with infarction, high grade obstructive lesions and, perhaps, without thrombosis. Platelet survival time in these patients is less often abnormal.

Other possible causes of infarction in absence of obstructive disease: In our patients we did not perform at cardiac catheterization any maneuver designed to provoke coronary spasm, and no patient had "spontaneous" coronary spasm at catheterization. Controversy continues to surround the idea that coronary spasm can result in myocardial infarction.[11] Our study does not provide any information relevant to the view that small vessel coronary disease can cause myocardial infarction. The data do provide some information to suggest that coronary thrombosis can cause infarction in patients subsequently shown to have a normal coronary arteriogram.

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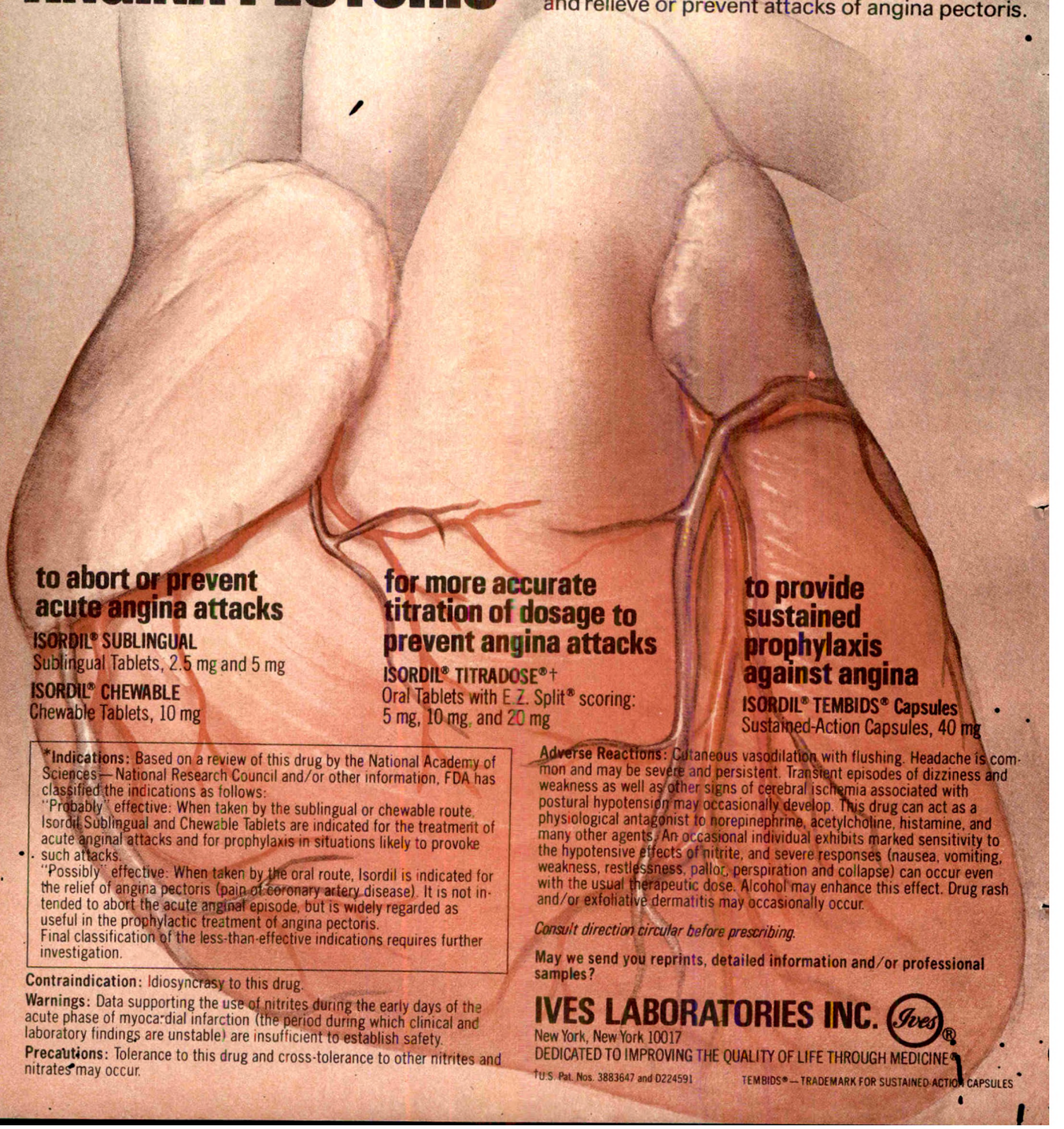
HELPS THE HEART IN THE CONTROL OF ANGINA PECTORIS*

The established use of Isordil in the management of angina pectoris for more than two decades has often been ascribed only to the vasodilatation it produces in the coronary arteries. Recent investigations, however, suggest that an even more important effect of this agent is to dilate peripheral arteries and veins. Arterial dilatation lowers impedance to left ventricular ejection, reducing afterload. Venous dilatation leads to venous pooling and a fall in right and left ventricular filling pressure, thus reducing preload.

With afterload and preload reduced, the amount of energy expended and oxygen consumed by the heart should be decreased. Isordil can thus reduce myocardial oxygen requirements and relieve or prevent attacks of angina pectoris.



to abort or prevent acute angina attacks

ISORDIL® SUBLINGUAL
Sublingual Tablets, 2.5 mg and 5 mg

ISORDIL® CHEWABLE
Chewable Tablets, 10 mg

for more accurate titration of dosage to prevent angina attacks

ISORDIL® TITRADOSE®†
Oral Tablets with E.Z. Split® scoring:
5 mg, 10 mg, and 20 mg

to provide sustained prophylaxis against angina

ISORDIL® TEMBIDS® Capsules
Sustained-Action Capsules, 40 mg

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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†U.S. Pat. Nos. 3883647 and D224591

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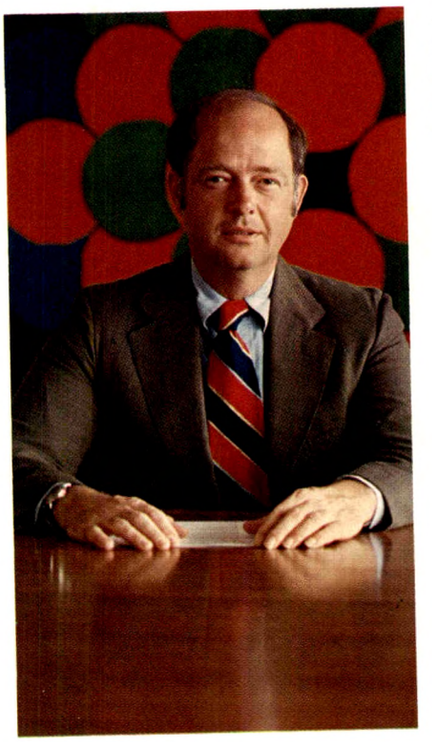
"How ARCO Medical Products Company is improving the predictability of cardiac pacing."



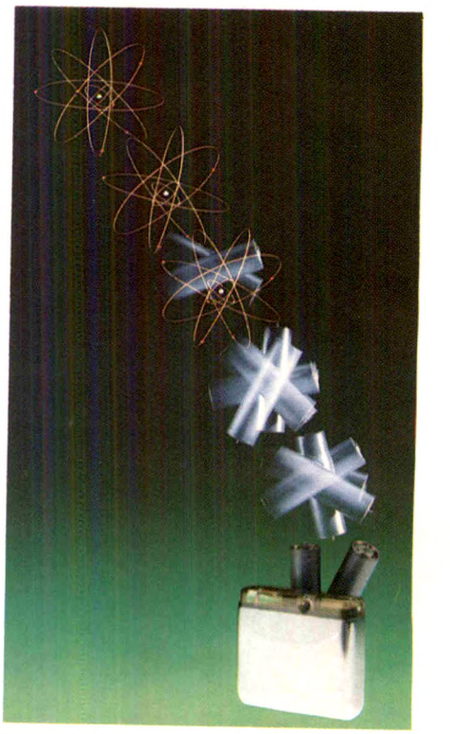
—an open letter to physicians and other members of the medical community from Page Thompson, President, ARCO Medical Products Company.

"ARCO Medical Products Company, a subsidiary of Atlantic Richfield Company—the 12th largest corporate entity in the United States, known principally for its chemical, petroleum and mineral operations—is now emerging as a leader in the highly specialized field of cardiac pacemaker systems. And we would like you to be sure that there are substantial benefits accruing to you and your patients due to our solid and rapidly growing position in this field.

"**To highlight a few of the benefits for you** we'd like to call your attention to the fact that ARCO Medical Products Company now provides:

- Pulse generators substantially improved in predictability
- A lithium thionyl chloride power source with highly desirable characteristics
- Significantly increased research and development to provide improved and new products in the near future
- A responsible attitude toward selling whereby we will not offer for sale what we cannot deliver—within 48 hours—anywhere in the free world
- Realistic, 'no-nonsense' product guarantees

"**To understand how it all began** look back to the early 1960s. Our people were then encapsulating nuclear materials used in the naval nuclear submarine program and the Apollo space program. As a result of this experience, we were awarded the first AEC contract for the encapsulation of nuclear material to be implanted in the human body. That was the beginning of the first nuclear-powered pulse generator.



"The precision and expertise put into the manufacture of those first nuclear-powered units is apparent when you see they have been functioning effectively for ten years, with a long life expectancy still ahead of them.

"**The nuclear experience evolved** into the development of pacemaker technology that utilized the nuclear-precise production and quality assurance techniques perfected when working on the AEC contract.

"ARCO Medical Products Company helped develop the advanced and exclusive lithium thionyl chloride power cell, which does not build up internal pressure. ARCO Medical

Products Company developed the triple encapsulation process which virtually solved the problem of invasion and migration of moisture within the generators.
ARCO Medical Products Company developed both a component and a total unit 'burn-in' process which virtually eliminates initial failures.
In these ways, and in many others, ARCO Medical Products Company has succeeded in significantly improving the predictability of the pulse generator.

"**We are a concerned company,** and this concern has led us to a commitment that no other pulse generator company matches: improved pulse generators

supported by a 'no-nonsense' product guarantee. In essence:

1. In the event an ARCOlith™ pulse generator becomes defective for any reason up to and including 60 days following implant, ARCO Medical Products Company will furnish a replacement pulse generator at no charge and pay *all* surgical and hospital costs as established by third-party insurance company pay schedules.*
2. In the event an ARCOlith pulse generator becomes defective for any reason after 60 days following implant up to the end of the warranty period,* ARCO Medical Products Company will furnish a replacement pulse generator at no charge and pay up to a total of $200 for surgical and hospital costs over third-party insurance company pay schedules.*

"**Be involved.** Take a stand by communicating your thoughts to us. Whatever your concerns may be regarding our products, our business philosophy, or your hopes for the future of pacemaker technology, we would like to hear from you. Kindly use the form on the following page to jot down your thoughts and mail them to me. It will be a pleasure to share your ideas."

Page Thompson

*Refer to warranty for complete details.

ARCOlith™ 12, 6, and 4 are now the trade names for pulse generator models LI-2, LI-4 and LI-3.

We'd like to hear from you.

ARCO Medical Products Company invites you to communicate your thoughts regarding implantable pulse generators or manufacturer-physician relationships.

Get involved. Take a stand. Tell us what's on your mind so we can be of better service to you and your patients in the future:

Page Thompson, President
ARCO/Medical Products Company
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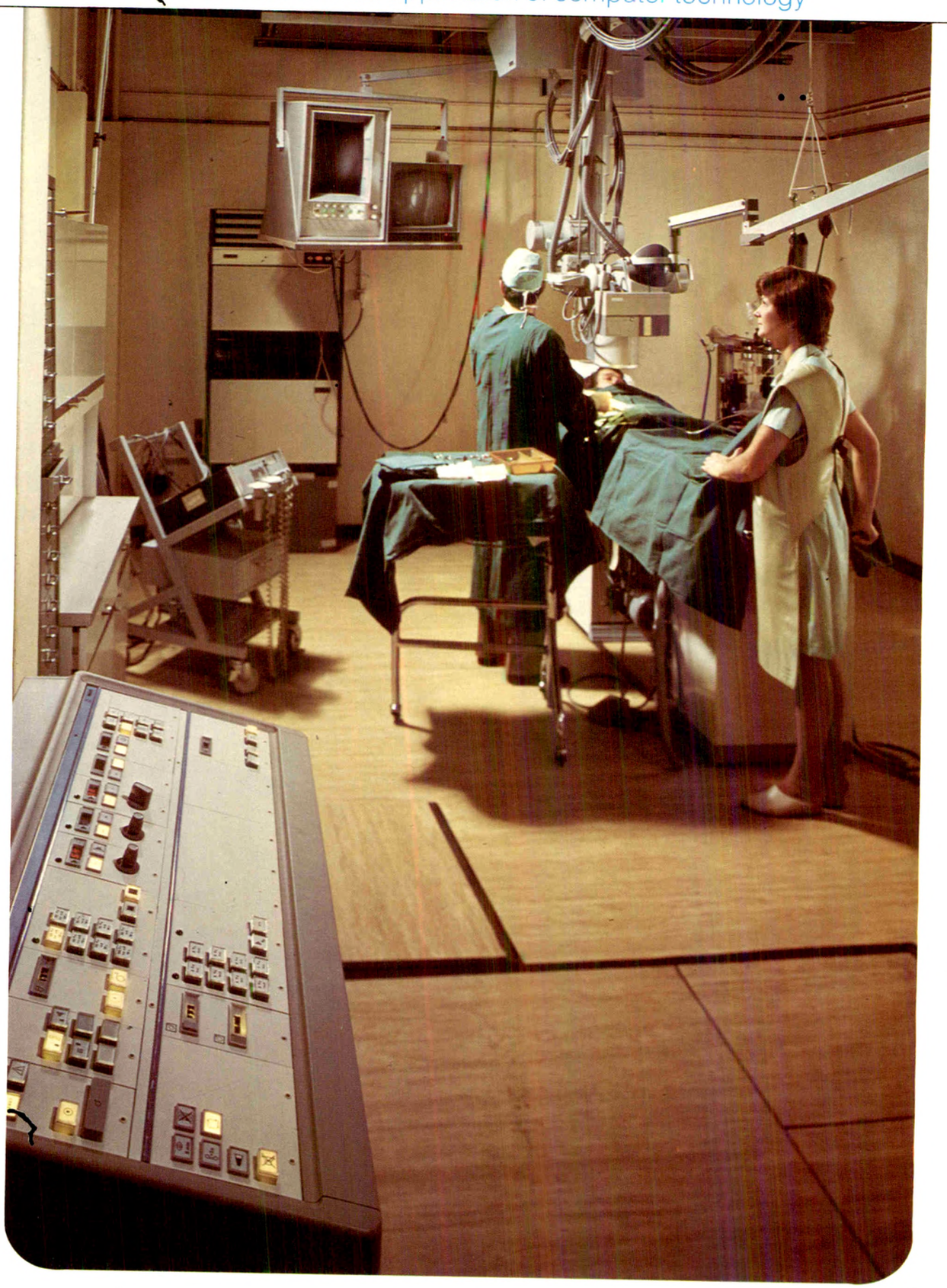

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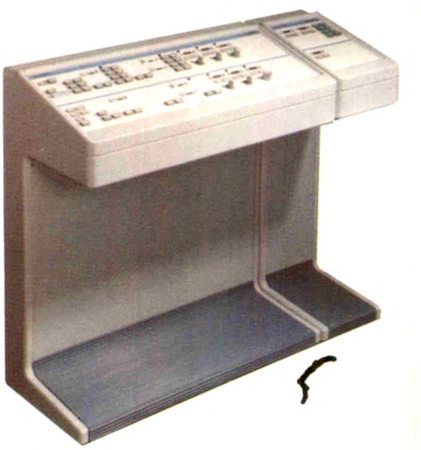

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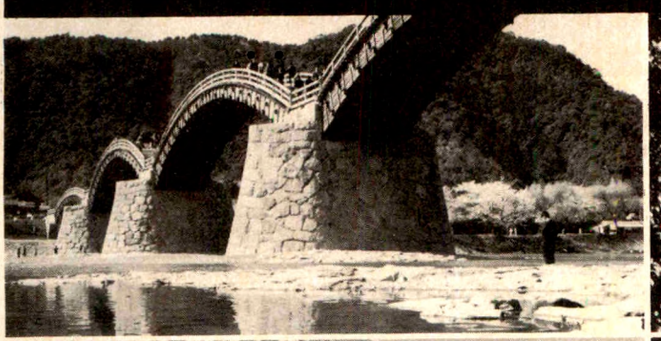

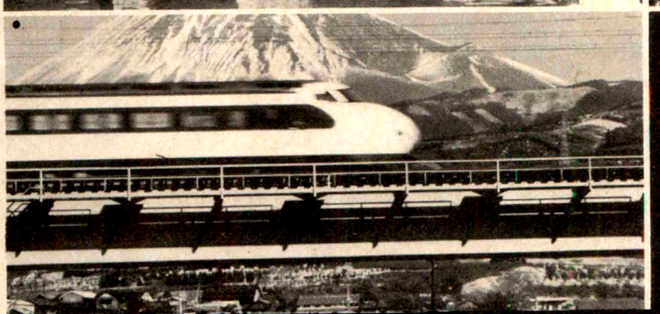

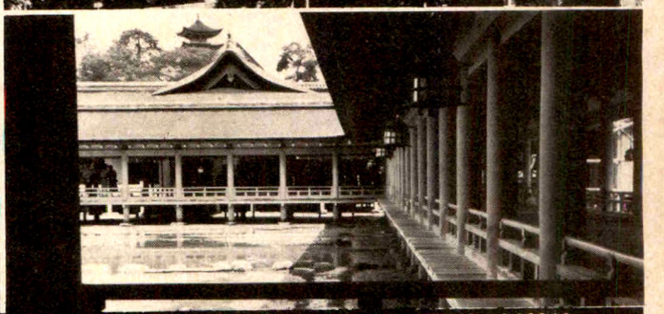

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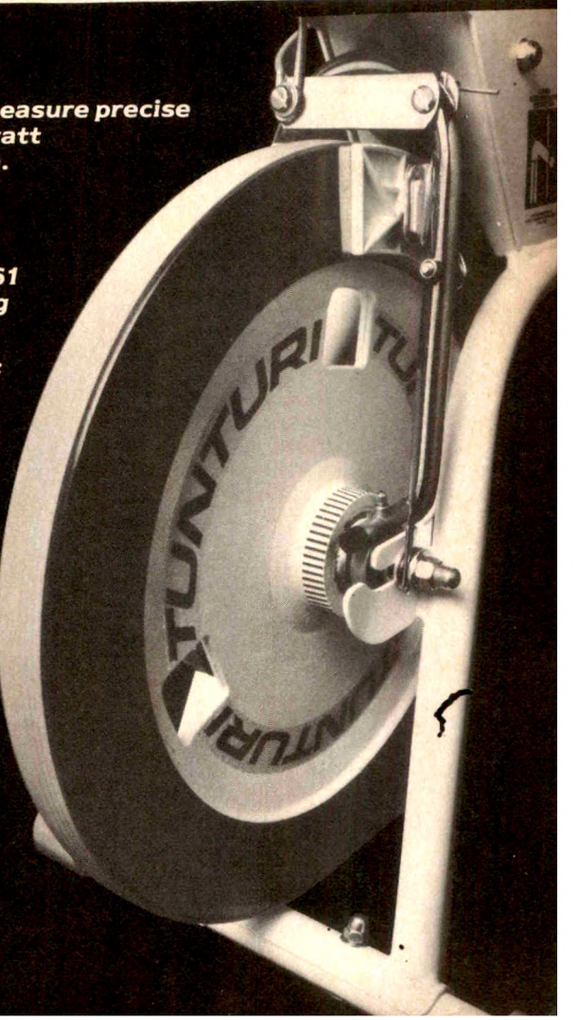

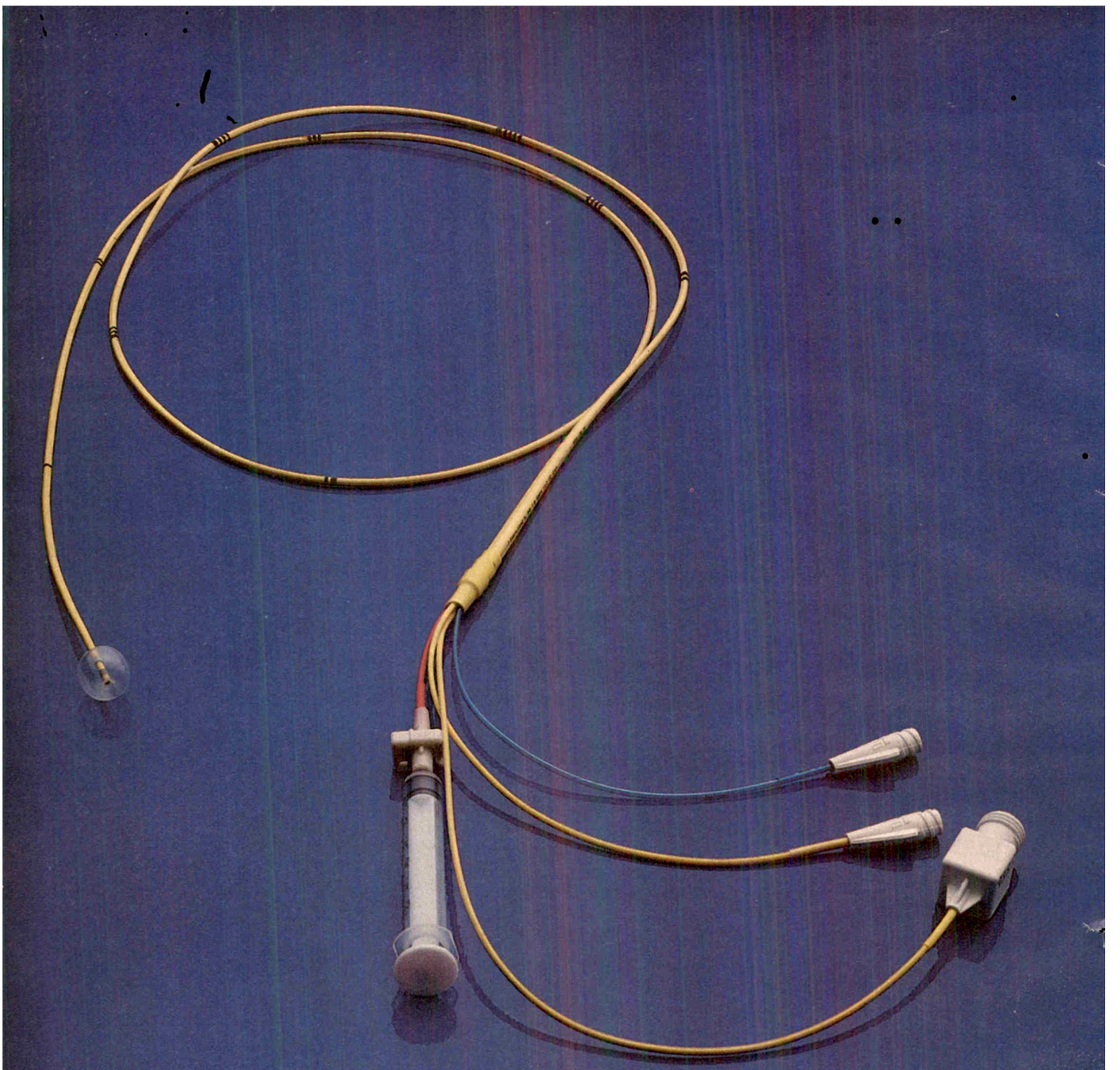

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before you prescribe these.

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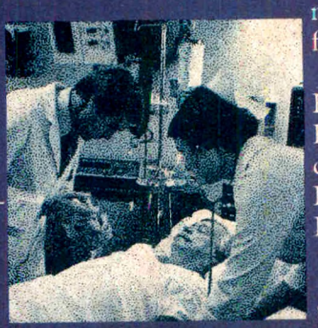

Ask your local Edwards' Technical Representative for copies, or contact: Edwards Laboratories, Division of American Hospital Supply Corporation, 17221 Red Hill Avenue (Irvine), P.O. Box 11150, Santa Ana, CA 92711, 714/557-8910, Cable Address: EDSLAB, Telex: 68:5567

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Automation solved one of their problems.

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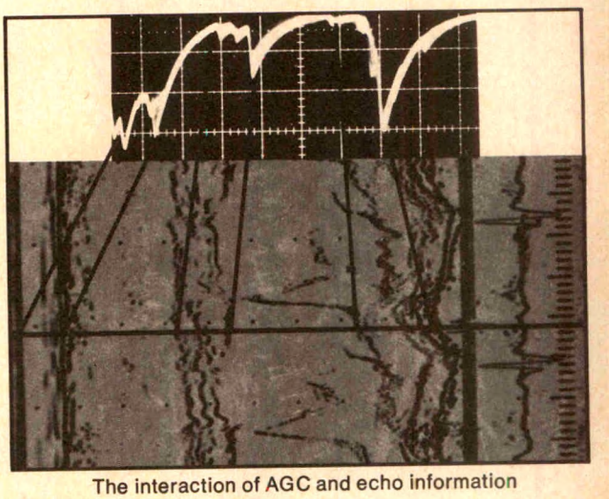
Automatic Gain Compensation (AGC) circuitry has been designed to automatically analyze and determine the optimum display of each returning echo, so that heart structures are clearly delineated. As moving structures change depth and angle, the real-time flexibility of AGC permits the display to remain true and accurate throughout the examination. The result: more clinical information and an extremely high percentage of interpretable exams.



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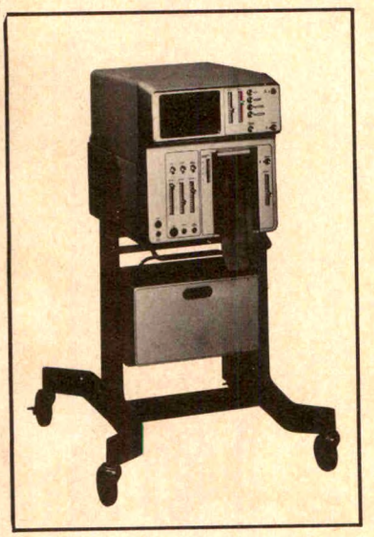

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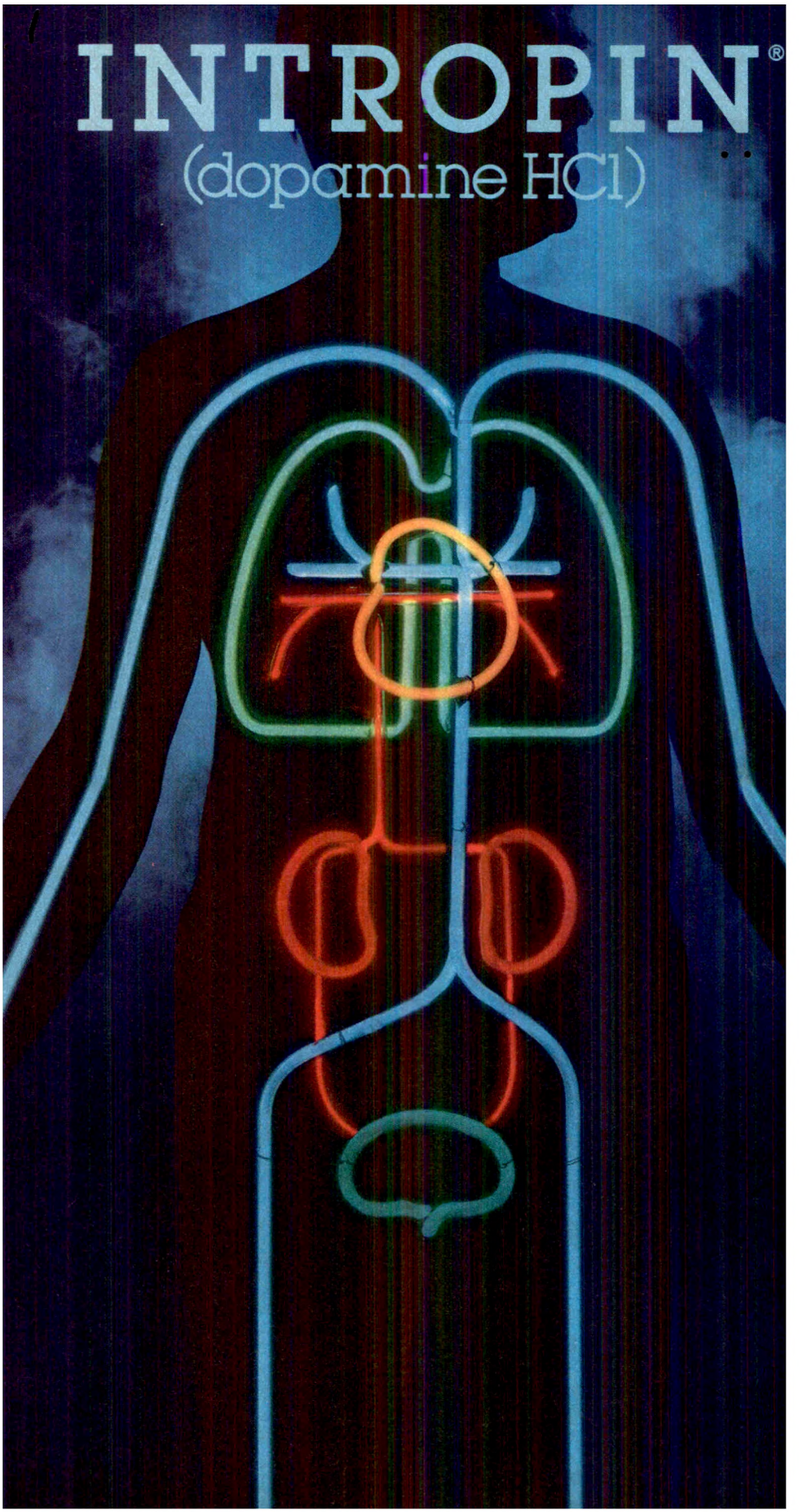

INTROPIN®
(dopamine HCl)

In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

Maintains kidney function

The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation

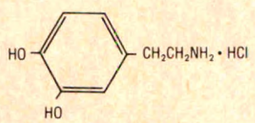
INTROPIN® (dopamine HCl)

(See last page of this advertisement for full prescribing information.)

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation

Effects of Ionophore RO 2-2985 (X537A) on Conscious Dogs in Experimentally Induced Hemorrhagic Hypotension

Mortality, Systemic Pressure and Renal and Coronary Blood Flow

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RO 2-2985, a potent inotropic agent, produces prolonged increases in left ventricular pressure and coronary and renal blood flow in conscious dogs. To evaluate these effects, 18 dogs were chronically instrumented with aortic or left ventricular pressure catheters, or both, and coronary and renal pulsed Doppler flow probes; 14 to 25 days later, after control values were recorded, sufficient blood was removed from each dog to reduce mean aortic pressure to 40 to 50 mm Hg or left ventricular pressure to 50 to 65 mm Hg during a 15 minute period. This pressure was maintained by withdrawal or addition of blood as necessary for an additional 30 minutes. The animals were then separated into two groups; one group was given RO 2-2985, the other an equivalent amount of drug solvent. Measurements were then made for 75 minutes or until death occurred. Retransfusion was performed in those animals living at 75 minutes. All 10 animals that received RO 2-2985 lived. After the drug injection, blood pressure and coronary and renal blood flow increased. Only one of eight animals receiving the solvent alone lived. The remaining control animals showed progressive deterioration in pressure and flow until death. The data show that RO 2-2985 decreased mortality and increased blood flow in the coronary and renal beds during hemorrhage-induced hypotension.

RO 2-2985 (X537A) (Hoffman-LaRoche) is an antibiotic drug that was originally isolated from a species of Streptomyces.[1] Pressman et al.[2–6] found that this compound and several others can form a complex with cations including catecholamines and can transport them across lipid membranes. RO 2-2985 produces a marked and prolonged positive inotropic and coronary vasodilator effect in the anesthetized dog.[7–9] Recently we studied the effects of this drug on myocardial function and regional hemodynamics in conscious chronically instrumented dogs.[10] In these animals, RO 2-2985 produced an inotropic effect and a large increase in coronary, renal and iliac blood flow. Coronary vascular resistance was not measured, but renal and iliac resistance levels decreased after administration of the drug. Anesthetized animals studied during hypotension induced by hemorrhage showed increases in systemic arterial blood pressure and renal blood flow and no change in renal vascular resistance in response to the drug.

These hemodynamic changes suggested to us that RO 2-2985 might be therapeutically useful during acute states of hypotension that accompany blood loss. However, the influence of anesthesia and acute operative conditions cannot be assessed, nor can potential effects of the drug on mortality be evaluated in this preparation. In addition, Vatner[11] clearly demonstrated that the renal hemodynamic alterations that occur in conscious dogs subjected to hemorrhage may differ in both magnitude and direction from the alterations found in anesthetized dogs.

The present study was designed to define more clearly the hemodynamic effects of RO 2-2985 during hemorrhagic hypotension and to identify potential clinical applications of the drug. Hypotension was

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This study was performed while Dr. Hanley was an Investigator, Howard Hughes Medical Institute.

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TABLE I

Individual Results in Control (Solvent-Treated) Group

Dog no.	Control	Post-Hemorrhage	Minutes After Drug Solvent 15	30	45	60	75
1							
Aortic pressure (mm Hg)	110	50	*	...	...	...	...
Coronary flow (cc/min)	46	31	...	...	...	...	...
Renal flow (cc/min)	158	29	...	...	...	...	...
2							
Left ventricular Pressure (mm Hg)	125	55	*	...	...	...	...
Coronary flow (cc/min)	50	15	...	...	...	...	...
Renal flow (cc/min)	...	...	...	...	...	...	...
3							
Aortic pressure (mm Hg)	115	55	50	35	*	...	...
Coronary flow (cc/min)	53	43	46	37	...	...	...
Renal flow (cc/min)	140	60	40	20	...	...	...
4							
Left ventricular pressure (mm Hg)	120	60	70	50	60	50	*
Coronary flow (cc/min)	...	...	...	...	...	...	...
Renal flow (cc/min)	162	18	18	18	18	18	...
5							
Left ventricular pressure (mm Hg)	150	55	*	...	...	...	...
Coronary flow (cc/min)	45	22	...	...	...	...	...
Renal flow (cc/min)	162	36	...	...	...	...	...
6							
Aortic pressure (mm Hg)	105	40	50	55	*	...	...
Coronary flow (cc/min)	43	9	34	31	...	...	...
Renal flow (cc/min)	162	36	18	18	...	...	...
7							
Aortic pressure (mm Hg)	85	40	45	45	55	55	50
Coronary flow (cc/min)	61	35	38	38	61	74	61
Renal flow (cc/min)	...	...	...	...	...	...	...
8							
Aortic pressure (mm Hg)	100	45	40	25	*	...	...
Coronary flow (cc/min)	...	...	...	...	...	...	...
Renal flow (cc/min)	160	80	100	20	...	...	...

* Death.

induced in conscious chronically instrumented dogs and the effect of RO 2-2985 on mortality, systemic pressure and renal and coronary blood flow was evaluated.

Methods

With use of sterile technique and pentobarbital anesthesia (30 mg/kg body weight) a left thoracotomy and left flank and right groin incisions were performed in 18 mongrel dogs weighing 25 to 35 kg. The heart was exposed, Tygon tubing was inserted into the left ventricular cavity through an apical stab wound and was secured in place with a purse-string suture. A short section of the proximal left circumflex coronary artery was dissected free 1 to 2 cm distal to the bifurcation of the left main coronary, and a pulsed Doppler flow probe[12,13] was placed around it. The left renal artery was identified using blunt retroperitoneal dissection through the left flank incision; a pulsed Doppler probe was placed around it, care being taken to preserve renal innervation. Tygon tubing was then inserted into the right femoral artery through the groin incision and

TABLE II

Comparative Results in RO2-2985-Treated Group (mean ± standard error of the mean)

	Control	Post-Hemorrhage	Minutes After RO 2-2985 15	30	45	60	75
Aortic pressure (mm Hg)	112 ±6	46 ±2	87 ±9	94 ±6	90 ±9	86 ±9	76 ±11
Left ventricular pressure (mm Hg)	107 ±5	54 ±2	102 ±11	101 ±5	101 ±4	90 ±5	79 ±8
Coronary flow (cc/min)	57 ±2	30 ±2	61 ±4	56 ±4	53 ±3	45 ±5	50 ±5
Coronary resistance (mm Hg/min per cc^{-1})	2.06 ±0.19	1.52 ±0.10	1.33 ±0.10	1.71 ±0.07	1.64 ±0.13	1.74 ±0.14	1.36 ±0.17
Renal flow (cc/min)	145 ±9	68 ±15	194 ±58	207 ±55	183 ±45	168 ±47	145 ±46
Renal resistance (mm Hg/min per cc^{-1})	0.71 0.06	0.94 ±0.35	0.59 ±0.21	0.54 ±0.13	0.57 ±0.10	0.58 ±0.10	0.93 ±0.45

was advanced in a retrograde manner to the level of the abdominal aorta and secured in place. All wires and tubing were then tunneled subcutaneously and exteriorized in the posterior cervical area. The incisions were closed, and during recovery (14 to 25 days) each animal was conditioned to the laboratory. Each animal was primarily cared for by the person who would later be responsible for its control during the actual experiment.

Protocol: On the day of the experiment the animal was positioned lying quietly on his right side. An intravenous catheter was inserted and advanced to a central location. The wires were connected to a multichannel pulsed Doppler flowmeter[12,13] for flow measurements, and the tubing was connected to Statham P23 Db transducers for pressure measurement. Data were recorded on an eight channel Brush recorder and stored on magnetic tape (Hewlett-Packard Corporation, model 3955). Mean values for flow and pressure were derived from the phasic signals electronically using resistance-capacitance filters with a 3 second time constant.

Control values were then recorded. Flow velocity contours were measured across the vessels and if either turbulence or poor signal to noise ratios were noted, data from the flow channel were discarded. Blood was then withdrawn rapidly from each animal in sufficient quantity over a 15 minute period to decrease mean aortic pressure to 40 to 50 mm Hg or (in animals in which only the left ventricular pressure catheter was functional) to a peak systolic pressure of 50 to 65 mm Hg. All 18 animals were maintained at this pressure for 30 minutes by the administration or withdrawal of blood as necessary.

Each animal was then randomly separated into one of two groups: (1) Group I (10 dogs) was given RO 2-2985 (1 mg/kg by intravenous injection), and (2) Group II (8 dogs) was given an equivalent amount of the drug solvent (a mixture of benzyl alcohol, propylene glycol and anhydrous alcohol) (0.2 cc/kg).

After the injection of either drug or solvent the intravenous tubing was clamped and the animals were studied for 75 minutes or until death. Those alive at 75 minutes underwent retransfusion with the withdrawn blood and were allowed to recover. During the shock period all animals showed signs of restlessness, pupillary dilatation and panting. Those that died progressed to an obtunded state before their death.

Blood flow measurements: When possible, blood flow was calibrated in vivo over a wide range of pressure and flow levels by cannulating the vessel distal to the flow probe and adjusting flow with use of a screw clamp. Flow was measured using a stopwatch and graduated cylinder. In experiments in which this was not possible flow levels were calibrated with use of a gravity drainage technique or from the Doppler equation. All three of these methods have been extensively tested and the results agree closely. During the 14 to 25 days after operation and before study the flow probes become encased in a fibrous capsule around the blood vessel. This development limits changes in geometric shape of that portion of the vessel directly under the probe.

Results

Post-hemorrhage period: The heart rate of the animals, measured at the beginning of each experiment, was 101 ± 5 beats/min (mean ± standard error of the mean). This increased to 159 ± 16 beats/min after hemorrhage and was not significantly changed thereafter by administration of RO 2-2985. The hemorrhage caused a decrease in mean aortic pressure, left ventricular systolic pressure, left circumflex coronary arterial blood flow and renal arterial blood flow. The values recorded before and after hemorrhage were: (1) mean aortic pressure 108 ± 4 to 46 ± 1 mm Hg, (2) left ventricular systolic pressure 118 ± 15 to 55 ± 2 mm Hg, (3) left circumflex coronary arterial blood flow 54 ± 2 to 28 ± 2 cc/min and (4) right renal arterial blood flow 152 + 5 to 54 ± 9 cc/min. All changes were highly significant ($P < 0.002$, paired Student's t test). Left circumflex coronary vascular resistance was 2.07 ± 0.20 mm Hg/min per cc^{-1} in the control state and 1.75 ± 0.94 after hemorrhage. The respective values for renal vascular resistance were 0.70 ± 0.01 mm Hg/ml blood flow per min and 1.01 ± 0.31. These values before and after hemorrhage were not significantly different ($P > 0.05$).

In the post-hemorrhagic period, immediately before injection of drug or solvent, the average values recorded from the animals that received RO 2-2985 were compared with those from the animals that received solvent. Mean aortic pressure, left ventricular systolic pressure, left circumflex coronary and renal blood flow and vascular resistance levels were not significantly different in the two groups.

Mortality after treatment: Mortality during the 75 minutes after the injection of drug or solvent differed greatly between the two groups. All 10 dogs treated with RO 2-2985 lived through the 75 minute post-injection period until retransfusion. Early in this investigation four of these animals were followed up for 2 weeks after retransfusion. All appeared to be in good health until they were killed. This follow-up period was not considered necessary in the remaining animals and if they appeared in good health, they were killed later in the day after retransfusion.

Seven of the eight dogs in the solvent-treated group died, five of these in the first 45 minutes after injection. This high early mortality rate left too few survivors late in the course of the experiments for meaningful statistical analysis of the data in this group. Thus the individual results of each dog in the solvent-treated group are listed in Table I, whereas the composite data for the drug-treated dogs are presented in Table II and Figures 1 and 2. The solvent has been used by us extensively in other experiments, has no sustained hemodynamic effects and has shown no evidence of toxicity.

Systemic pressure and blood flow measurements after treatment: With the exception of the one dog in the solvent-treated group that lived through 75 minutes, no dog in this group showed sustained improvement in either pressure or coronary or renal blood flow before death (Table I). In contrast, in the drug-treated group all these measurements were significantly increased over values in the post-hemorrhage period preceding drug injection (Table II, Fig. 1 to 3). The coronary and renal pressure-flow relations in the individual animals were such that, after the injection of the drug, both coronary and renal vascular resistance levels significantly decreased ($P < 0.05$ at 15 minutes).

Upon retransfusion, mean aortic pressure, left ventricular pressure and coronary blood flow increased over values during the original control state before hemorrhage ($P < 0.001$). Renal blood flow, already not signif-

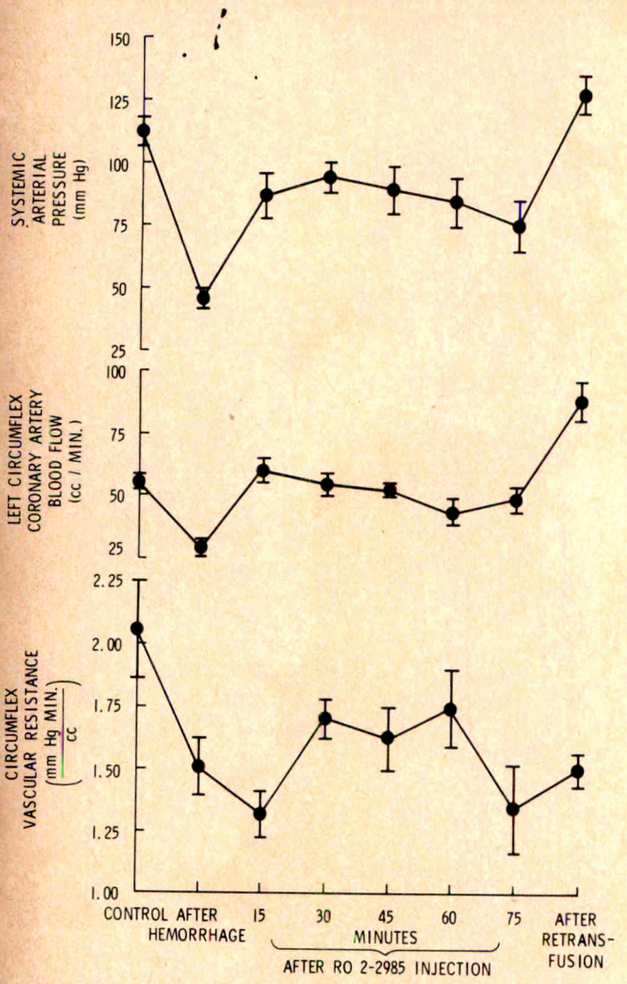

FIGURE 1. Effect of administration of RO2-2985 on systemic arterial pressure, circumflex coronary artery blood flow and circumflex vascular resistance after hemorrhagic hypotension was induced in conscious dogs. The bars in this and subsequent figures indicate standard error of the mean.

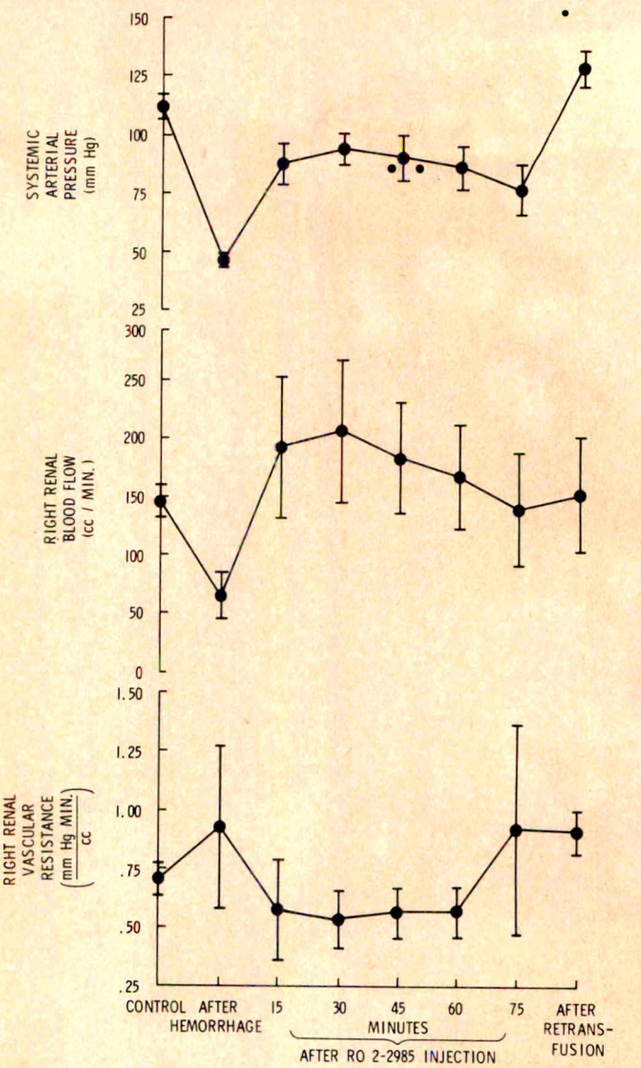

FIGURE 2. Effect of RO2-2985 administered during hemorrhagic hypotension on renal hemodynamics in 10 conscious dogs.

icantly different from values in the pre-hemorrhagic control state, did not change. After these initial retransfusion data were obtained, the hemodynamic measurements were discontinued.

Discussion

The data show that the ionophore RO 2-2985 significantly reduces mortality in a conscious canine model of hemorrhagic hypotension. The hemodynamic data are consistent with this finding because the drug produced marked improvement in arterial pressure and coronary and renal blood flow during the post-hemorrhagic state. These results were obtained in conscious unsedated chronically instrumented animals under conditions in which anesthesia and acute operative interventions could not be of influence.

The effects of the drug on arterial pressure and coronary and renal blood flow levels were directionally similar to the responses we reported for anesthetized animals with hemorrhagic hypotension,[10] but the renal vascular response differed. In the present study we found renal vasodilatation after administration of RO 2-2985 during hemorrhagic hypotension although we found no changes in renal vascular resistance in the study using anesthetized animals. Others[14,15] have also reported differences in renal vascular responses between awake and anesthetized preparations. The renal vascular bed has also been shown to respond differently to prostaglandin-inhibiting drugs when awake and anesthetized dogs were compared.[16] Both anesthesia and surgery are themselves major interventions, and differences in vascular responsiveness as a result of these procedures are to be expected.

Comparison with present studies: The findings of the present study require consideration in relation to other studies of hemorrhagic hypotension utilizing conscious dog models. Granata et al.[17] found an early increase, followed by a decrease in coronary vascular resistance, during progressive hemorrhage in conscious dogs. The hemorrhage produced in their study was over

a longer period of time (2 hours versus 15 minutes) and was slightly more severe (systemic arterial pressure of 35 to 45 mm Hg versus 40 to 55 mmHg) than in our study. This may explain the differences between their results and our own, in that we did not find a significant change in coronary vascular resistance with the shorter period of hemorrhage used in our study. The variable response of renal resistance found in our study is consistent with the results reported by Vatner.[11]

With the exception of the duration of drug effects, our data during hemorrhagic hypotension show directionally similar hemodynamic changes to those we found when the drug was administered to healthy conscious chronically instrumented dogs.[10] The total duration of vascular effects of the RO 2-2985 was not measured in the present experiments. However, the time to peak effect on both systemic arterial pressure (30 versus 60 minutes) and renal blood flow (30 versus 195 minutes) was shorter in the dogs with hemorrhagic hypotension than in healthy conscious dogs. The dogs treated with only the solvent illustrate the deteriorating hemodynamic state produced by this level of hemorrhagic hypotension. It is not surprising that the peak hemodynamic effects of a drug under such conditions would occur earlier than when the drug is given under conditions of circulatory stability.

Mechanism of hemodynamic effects: The mechanism by which RO 2-2985 produces these hemodynamic effects is not known. In healthy conscious chronically instrumented dogs the effects of the drug are clearly different from those found after injection of norepinephrine, epinephrine, isoproterenol or digitalis.[10] Furthermore, we have found that neither alpha adrenergic, muscarinic nor histaminergic receptor blockade totally blocks the effects of the drug[9,18] (and unpublished data). Pretreatment with reserpine blocks the inotropic, chronotropic and pressor effects of the drug; however, in dogs previously adrenalectomized and pretreated with 6-hydroxydopamine, RO 2-2985 exerted its usual hemodynamic effects[10] (and unpublished data).

A particularly intriguing action of the drug is its effect on the coronary vasculature.[18] Our previous studies[10,18] suggest that the increase in coronary blood flow produced by the drug is primary in nature and not merely a reflection of increased myocardial oxygen demand. It begins before the inotropic effect of the drug, peaks earlier and decreases while the pressure and the rate of rise of left ventricular pressure (dP/dt) are still increasing.[10] Pretreatment with reserpine does not block this effect of RO 2-2985 on coronary blood flow.[10]

This study has focused on the effects of the drug rather than on the mechanism by which they occur. Osborne et al.[19] recently demonstrated that this drug produces a translocation of large volumes of blood to the central circulation with a decrease in total body venous compliance. Some preliminary data obtained during our study support this finding. Two of the dogs studied, in addition to the instrumentation described, had ultrasonic segment length gauges implanted in the wall of the myocardium. These gauges measure regional myocardial dimensions. In these two dogs, after administration of RO 2-2985, end-diastolic length increased as measured by these crystals. Other inotropic agents have not been of particular value in the treatment of hemorrhagic hypotension and in some studies have had deleterious effects.[20] It may be that it is the combined effects of inotropic stimulation and increased central blood volume that are responsible for the results we have found.

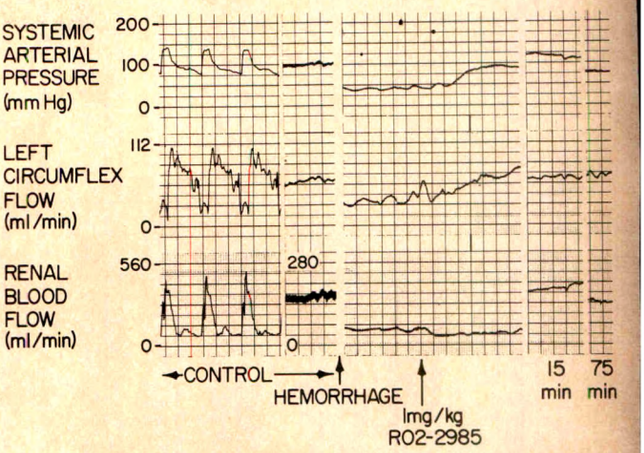

FIGURE 3. A typical recording of arterial pressure, circumflex coronary flow and renal blood flow (measured with the pulsed Doppler technique) in a conscious chronically instrumented dog before and after severe hemorrhage and after administration of RO2-2985. Note the change in scale in Panel 2.

Therapeutic implications: All animal models have limitations with regard to the simulation of clinical pathologic conditions, and data from animal studies should be extrapolated with extreme caution. Nevertheless, the striking decrease in mortality produced by RO 2-2985 in these studies, as well as the beneficial hemodynamic effects measured in two vital vascular beds critically comprised during severe hypotension, suggest that this type of chemical structure or a derivative of it may be clinically useful in combination with volume replacement in the therapy of acute hemorrhagic hypotension.

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Bruce Treadmill Test in Children: Normal Values In a Clinic Population

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The Bruce treadmill protocol is suitable for children as young as age 4 years. Maximal endurance time may be used as the sole criterion of exercise capacity, and normal values were established with 327 children having an innocent heart murmur. Mean endurance time in boys increased from 10.4 minutes at age 4 to 5 years, to 14.1 minutes at age 13 to 15 years. Mean endurance time in girls increased from 9.5 minutes at age 4 to 5 years to 12.3 minutes at age 10 to 12 years. Mean maximal heart rate ranged from 193 to 206 beats/min. Age differences in mean maximal and submaximal heart rates were small. There were negative correlations between endurance time and the ratio of weight to height^3. There were negative correlations between heart rates at treadmill stages 1 to 3 and the endurance times. The correlation coefficient of endurance time with maximal oxygen uptake was 0.88, but for clinical purposes endurance time alone is a satisfactory indicator of exercise performance.

The Bruce treadmill test is a commonly used exercise test to assess exercise capacity and the electrocardiographic response to exercise stress in adults.[1] The test protocol calls for 3 minute stages of increasing belt speed and percent grade on a treadmill and is suitable for maximally stressing patients whose exercise capacity is as low as 5 mets* or as high as that of endurance-trained athletes. Extensive use of this test in a pediatric cardiology department has shown the test to be suitable for children aged 4 years and older. This report reviews some test results in normal children and youths aged 4 to 18 years.

Methods

Treadmill protocol: The treadmill was programmed for increases in grade and speed every 3 minutes as outlined by Bruce et al.[1] (Table I). Calibrations for grade and belt speed were checked at frequent intervals. The children were tested at the time of visiting a cardiac clinic. They had no prior experience with the treadmill and no opportunity for practice. Most were purposely tested in the absence of their parents. Each child was urged to continue to the point of severe fatigue and, with experience, the laboratory technicians and nurses became expert at persuading the small and sometimes reluctant young children, or the larger and sometimes apathetic adolescents, to perform maximal or at least very close to maximal exercise. The end point of the test was a refusal to do more work despite verbal encouragement. This was manifested by the child's hanging on to the guard rails and refusing to let go on his jumping off, pushing the emergency stop button or going limp in the arms of the supervisor. The test results of six children aged 4 and 5 years and three teenage girls have not been included because the supervisor believed that these nine children had not produced a near maximal effort.

Lead CM_5 of the electrocardiogram was recorded at the end of each exercise stage, at the end of maximal exercise and at 2 and 5 minutes of the recovery period. Heart rate was obtained by measuring the interval between five R waves.

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* 1 met = resting metabolic rate = considered equal to an oxygen uptake of 3.5 ml/kg body weight per min.

TABLE I

Bruce Treadmill Test Protocol

Stage	Speed (miles/hour)	Grade (%)	Approximate Oxygen Cost (ml/kg per min)	Equivalent Ergometer Loads (kilopond-meters/min per kg body weight)
1	1.7	10	18	7
2	2.5	12	25	11
3	3.4	14	36	16
4	4.2	16	46	21
5	5.0	18	56	26
6	5.5	20	63	30
7	6.0	22	?70	34

No child was permitted to hold on to the guard rails for more than a few seconds to get his balance or for more than 5 seconds at the end of each exercise stage when the electrocardiogram was being recorded. Holding on materially reduces the metabolic cost of the work and adds considerably to the work time, even when only a few fingers are used. We did not use a harness for safety purposes because in the Bruce test the belt speed is low and an occasional fall has not been harmful. A technician was always available beside the child for support and to push an emergency stop button on the guard rail. All tests were performed in an air-conditioned laboratory at 19° C and 40 percent relative humidity. Reproducibility tests were carried out with 20 schoolchildren aged 7 to 13 years who repeated the test 3 to 10 days after the their first test.

Direct measurements of *maximal oxygen uptake* ($\dot{V}O_2$ max) were made in another group of 77 children by obtaining school volunteers and young athletes. Endurance times of these additional subjects were not included in the percentile calculations. In 38 of the schoolchildren oxygen uptake was measured during the last minute of each exercise stage and during the last few minutes of maximal exercise by collecting expired air in a Tissot spirometer and analyzing for oxygen and carbon dioxide with calibrated analyzers. There may be some controversy over the supervision of maximal exercise tests. In this laboratory all tests are carried out by trained technicians, usually in the absence of a physician. A physician is within 30 seconds call and reach of the laboratory for subjects with cardiovascular disease but not for normal children.

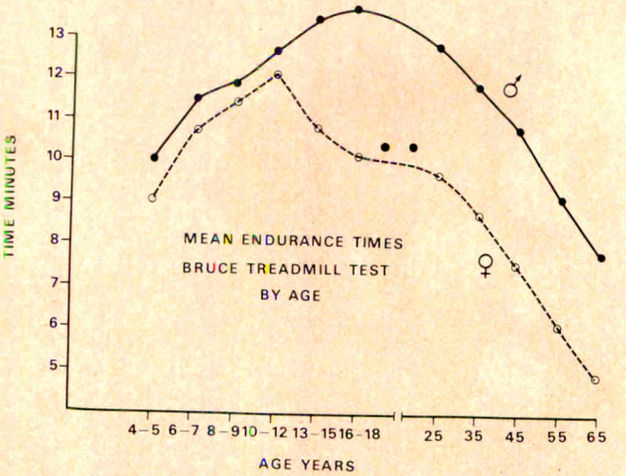

FIGURE 1. Mean endurance time by age for male and female subjects aged 4 to 65 years. For ages 4 to 18, values were taken from clinic patients with normal murmurs. For ages 25 to 65, male values were taken from volunteers in a normal male population. Each point is the mean of at least 60 subjects. For ages 25 to 65, female values were taken from the data of Bruce et al.[1]

Subjects: All 327 subjects tested had been referred to a cardiac clinic where a definite diagnosis of innocent murmur was made. This diagnosis was established on the basis of clinical findings, resting electrocardiograms in all subjects and chest roentgenograms in some.

Results

Endurance time: Percentile values for endurance times were established from a total number of 327 children divided into six age groups (Table II). The 50 percentile values increased in girls aged 4 to 7 years, leveled off for those aged 8 to 15 years then decreased in the older girls. For the boys the 50 percentile values

TABLE II

Bruce Treadmill Test Endurance Times (min) in Clinic Children With an Innocent Murmur

Age Group (yr)	no.	Percentiles 10	25	50	75	90	Mean	SD
				Boys				
4–5	40	8.1	9.0	10.0	12.0	13.3	10.4	1.9
6–7	28	9.7	10.0	12.0	12.3	13.5	11.8	1.6
8–9	30	9.6	10.5	12.4	13.7	16.2	12.6	2.3
10–12	31	9.9	12.0	12.5	14.0	15.4	12.7	1.9
13–15	26	11.2	13.0	14.3	16.0	16.1	14.1	1.7
16–18	12	11.3	12.1	13.8	14.5	15.8	13.5	1.4
				Girls				
4–5	36	7.0	8.0	9.0	11.2	12.3	9.5	1.8
6–7	34	9.5	9.6	11.4	13.0	13.0	11.2	1.5
8–9	26	9.9	10.5	11.0	13.0	14.2	11.8	1.6
10–12	28	10.5	11.3	12.0	13.0	14.6	12.3	1.4
13–15	24	9.4	10.0	11.5	12.0	13.0	11.1	1.3
16–18	12	8.1	10.0	10.5	12.0	12.4	10.7	1.4

no. = number of subjects; SD = standard deviation.

TABLE III

Achieved Heart Rates (beats/min) for the Bruce Treadmill Test (mean ± standard deviation)

Age Group (yr)	Rest	Stage 1	Stage 2	Stage 3	Stage 4	Maximal	Recovery* R2	Recovery* R5	Lowest Maximal
Girls									
4–5	102 ± 19	144 ± 13	173 ± 19	195 ± 14	. . .	199 ± 10	128 ± 19	121 ± 12	183
6–7	102 ± 19	136 ± 20	163 ± 18	196 ± 6	. . .	206 ± 4	141 ± 18	132 ± 15	193
8–9	79 ± 13	117 ± 17	144 ± 17	180 ± 13	198 ± 6	202 ± 9	121 ± 16	112 ± 14	188
10–12	84 ± 13	126 ± 11	150 ± 13	188 ± 11	197 ± 5	204 ± 8	134 ± 18	122 ± 12	188
13–15	85 ± 12	127 ± 19	153 ± 18	180 ± 16	186 ± 11	196 ± 6	128 ± 21	117 ± 18	180
16–18	92 ± 12	134 ± 15	164 ± 19	186 ± 9	. . .	193 ± 5	142 ± 18	124 ± 13	186
Boys									
4–5	97 ± 13	135 ± 15	161 ± 17	189 ± 13	194 ± 6	200 ± 9	121 ± 16	114 ± 10	180
6–7	92 ± 14	131 ± 12	154 ± 12	188 ± 12	203 ± 14	201 ± 7	125 ± 13	116 ± 17	183
8–9	84 ± 13	127 ± 10	146 ± 15	177 ± 12	198 ± 8	200 ± 6	122 ± 11	116 ± 9	183
10–12	84 ± 15	122 ± 11	140 ± 12	174 ± 13	194 ± 9	199 ± 7	125 ± 11	116 ± 10	180
13–15	72 ± 9	112 ± 12	129 ± 14	163 ± 14	191 ± 10	198 ± 6	122 ± 13	112 ± 13	188
16–18	77 ± 10	105 ± 15	137 ± 18	174 ± 12	189 ± 7	201 ± 6	138 ± 14	127 ± 10	183

* R2 and R5 = recovery at 2 and 5 minutes sitting with feet elevated.

increased from age 4 and 5 years to age 8 and 9 years, then increased more gradually thereafter to reach peak values at age 13 to 15 years. The 10 and 25 percentile values were disproportionately lower for children in the younger and older age groups, possibly because some of these subjects could not be motivated to work maximally.

Mean average endurance times for ages 4 to 65 years are shown in Figure 1. Values for adult men were taken from an ongoing survey of a normal population being studied in this laboratory[2] and are similar to values reported by Bruce et al.[1] for Seattle men. Values for adult women were taken from the report of Bruce et al.[1] For male subjects the mean endurance time at age 8 years was the same as that at age 35; at age 6 it was equal to that at age 40 and at age 4 to 5 was equal to that at age 50. For female subjects the mean endurance time in 4 and 5 year olds was better than that recorded after age 35, and the mean time at age 6 and 7 was better than that recorded for female subjects aged 13 years and older. The mean values for girls were similar to those of boys up to age 12 years, differing by only 30 to 45 seconds; after age 12 the gap widened. The mean endurance time at age 16 to 18 years was 35 percent longer in the male subjects, and at age 55 the difference was 55 percent. In the children the endurance time represents the maximal time they would work with the technicians, who usually were able to encourage them to continue a few minutes after they wanted to stop; middle-aged adults were not encouraged to the same degree. Because of the selection methods, the values in Figure 1 are not reliable norms for the population at large but are shown for comparative purposes.

Heart rate: Table III and Figures 2 and 3 show the mean heart rates of the various age groups at rest, at each exercise stage and during recovery. The mean heart rates were similar in most age groups. For both boys and girls the resting and exercise rates were fastest in the youngest age group. The mean maximal heart rate of the various age groups ranged from 193 to 206 beats/min. For stages 1 to 3 the 13 to 15 year old boys had the lowest heart rate. The 16 to 18 year old boys had the highest recovery rates and there were only slight differences in the mean rates for the other age groups. If fitness for submaximal exercise is judged on the basis of the lowest heart rate for submaximal work, then boys were most fit at age 13 to 15. Some children, particularly girls, had a heart rate of up to 190 beats/min during stage 2 of the test and yet were capable of completing stages 3 and 4 and had a final maximal heart rate of 200 to 220 beats/min. The lowest maximal heart rate by age group ranged from 180 to 193 beats/min, and the highest from 203 to 220.

Correlation of heart rate and endurance time: There were significant negative correlations between the heart rates for stages 2 and 3 of the Bruce test and the endurance times. Not unexpectedly, subjects with a slower heart rate during the submaximal portions of the test had a longer endurance time. The correlation coefficients for the various age groups and sexes ranged from 0.20 to 0.77 (Table IV). These correlations would

TABLE IV

Correlation Coefficients of Endurance Time versus Heart Rate for Stage 2 of Bruce Test

Age Group (yr)	Correlation Coefficients (r) Girls	Boys
4–5	−0.55†	−0.20*
6–7	−0.61†	−0.30*
8–9	−0.68†	−0.77†
10–12	−0.40†	−0.60†
13–15	−0.59†	−0.01
16–18	−0.42†	−0.40†

* $P < 0.05$.
† $P < 0.01$.

allow the prediction of maximal performance from submaximal heart rate as is done with bicycle ergometer work.[3]

Oxygen uptake: Age differences in the oxygen uptake ($\dot{V}O_2$) during the 3rd minute of stages 1 to 3 of the Bruce test are present as indicated in Table V. The lowest age group tested, the 7 year olds, had the highest $\dot{V}O_2$ values (6 to 20 percent above adult values); by age 11 to 12 years the values for children were only 1 to 6 percent higher than those reported for adults by Bruce et al.[1] The oxygen costs of stages 4 and 5 have not been listed because only a few subjects went on to complete

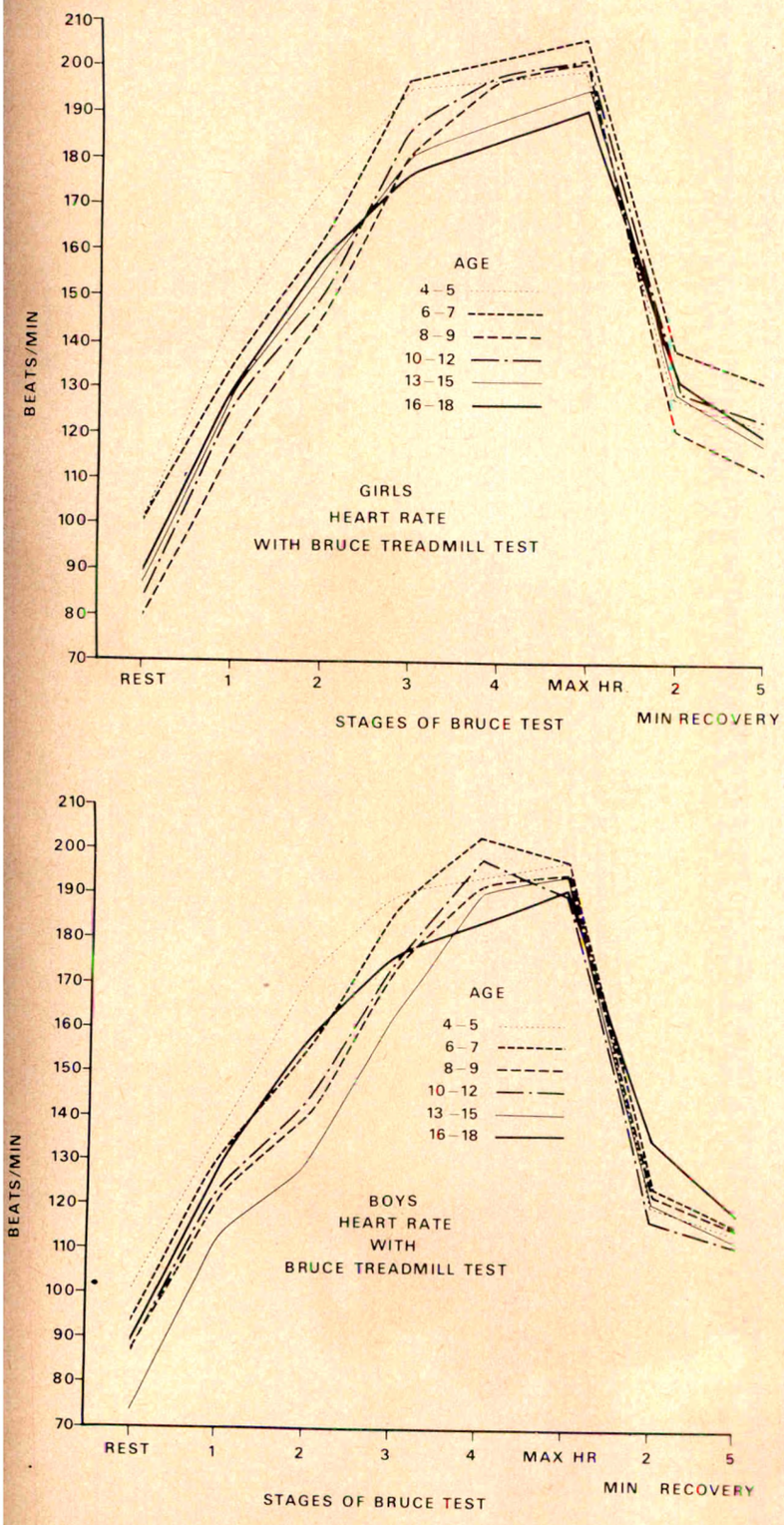

FIGURE 2. Mean heart rate during and after the Bruce treadmill test. **A,** in girls with a normal murmur. **B,** in boys with a normal murmur. MAX HR = maximal heart rate; MIN = minutes.

at least 2 minutes of the next load, a minimal requirement to ensure that the cost of the stage in question was not greater than the person's maximal $\dot{V}O_2$. In 36 athletes aged 13 to 20 years we found the oxygen uptake during the 3rd minute of stage 4 to be 46.9 ± 2.7 ml/kg per min (mean ± standard deviation), and of stage 5 to be 56.5 ± 3.1 ml/kg per min.

The ratio of weight to height[3] was used as an index of heaviness. Linear regression studies showed that in each age group there was a negative correlation between endurance time and this ratio, the correlation coefficients ranging from 0.20 to 0.47. These correlations were of low order but were statistically significant ($P < 0.05$).

Data on maximal oxygen uptake and endurance time were collected from an additional 53 girls and 24 boys (not included in the percentiles for endurance time). There was a close correlation between maximal $\dot{V}O_2$ and endurance time. The values for the girls are shown in Figure 3. For boys the correlation coefficient between endurance time and maximal $\dot{V}O_2$ was 0.85.

Comparison with bicycle ergometer: Many reports of exercise capacity in children have utilized the bicycle ergometer as the test device. Average boys reach stage 5 of the Bruce test; to achieve the equivalent metabolic load on the ergometer the 25 kg child must work at 640 kilopond-meters/min, and the 50 kg child at 1,300 kilopond-meters/min, or about 25 kilopond-meters/min per kg, a very difficult load to sustain. The equivalent bicycle loads in kilopond-meters/min per kg for the various stages of the Bruce test are given in Table I.

Reproducibility tests: Twenty normal schoolchildren aged 7 to 13 years performed the Bruce test on two occasions 3 to 10 days apart, neither they nor the examiner being aware of the time achieved on the first test. Endurance time ranged from 10.4 to 17.5 minutes; the mean times were 13.9 ± 2.1 for trial 1 and 13.7 ± 1.9 minutes for trial 2, and the linear regression of time 1 on time 2 gave a correlation coefficient of 0.94. The test was highly reproducible in this limited subsample of children.

Discussion

No magic formula was used in the design of the Bruce protocol; comfortable combinations of grades and belt speeds were chosen to provide light, moderate and maximal exercise stresses. Other suggested protocols[4–6] may be equally satisfactory. However, a modified Balke test[4] using 2 or 2.5 miles/hour and grade increments of 1 percent starting at 7 percent grade was tried in our laboratory in 150 children aged 4 to 6 years; the test was not as suitable as the Bruce test for fit cooperative children because it lasted too long, boredom became a factor, and the grade became too steep before exhaustion occurred. The method of Taylor et al.[7] of performing a maximal oxygen uptake test has been used in our laboratory for children aged 11 to 16 years, but this protocol requiring running at 6.5 miles/hour was not suitable for younger children. Because of the wide acceptance and popularity of the Bruce test for adults, it was decided to use this test as a start toward standardization of all clinical stress testing in our laboratory.

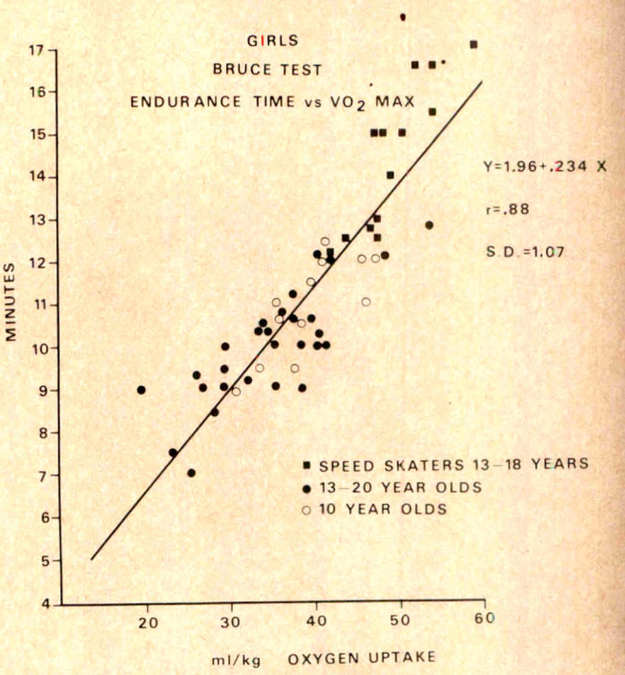

FIGURE 3. Endurance time on the Bruce treadmill test versus maximal oxygen uptake ($\dot{V}O_2$ max) obtained during the same test in three groups of subjects: 12 girl volunteers, aged 10 years, from a grade 5 school class; 13 girls, aged 13 to 18 years, training for competitive speed skating; 28 girls, aged 13 to 20 years, attending normal school classes or working in a hospital.

Determinants of exercise endurance time: The

TABLE V

Oxygen Uptake During the 3rd Minute of the Bruce Treadmill Test Stages 1 to 3 (in ml/kg per min [mean ± standard deviation])

	Age Group (yr)					
	7 (no. = 4)	9–10 (no. = 11)	11–12 (no. = 12)	13–14 (no. = 11)	Adults* (no. = 21–69)	Adults* (no. = 31–142)
Stage 1	20.2 ± 2.2	18.6 ± 2.1	18.1 ± 2.5	18.2 ± 1.5	17.4	12.1
Stage 2	26.4 ± 2.5	25.5 ± 2.9	24.3 ± 2.4	25.9 ± 2.9	24.8	24.0
Stage 3	40.2 ± 0.4	36.5 ± 5.3	35.2 ± 3.2	37.7 ± 3.5	34.3	33.3

* Data from Bruce et al.[1]

endurance time achieved is a result of many factors. It is obviously dependent on the motivation of the child to work to near exhaustion and on the skill of the technicians in the handling of young children. Physiologic factors that allow longer endurance times include aerobic and anaerobic power. The anaerobic component of a progressive test of 10 to 20 minutes' duration is mainly dependent on the ability of the working muscles to form lactate from glycogen during the last few minutes of exercise. This power may be less in prepubertal children because of a lower muscle glycogen content and a lower concentration of the enzyme phosphofructokinase.[8] The anaerobic system may be totally depleted of energy sources after 1 minute of supermaximal work,[9] so that differences in anaerobic power would not account for major differences in endurance times with the Bruce test, which lasted 9 to 18 minutes.

Aerobic power is dependent on the pumping capacity of the heart, the normal function of the lungs, the oxygen carrying capacity of the blood and the perfusion and oxidative metabolism in the working muscles. The efficiency of treadmill walking and running is said to be roughly equal in different subjects, but Table II indicates that there is a coefficient of variation of about 10 percent in the oxygen cost of submaximal exercise. Some of this variation is due to measurement error; some is due to interindividual differences in efficiency. There also were age differences in efficiency, and children at age 7 were up to 15 percent less efficient than older children. Two children of the same age and size may have differing abilities to walk and run on the treadmill because of unknown factors ("treadmill and running know-how"), and these differences may not be associated with measurable differences in energy metabolism. We have been impressed that children who are lean and wiry and tall for their age have a longer endurance time than soft or pudgy children, but the correlation studies using the crude measure of weight/height^3 as an indication of body build showed that build differences explained only about 16 percent of the interindividual variation in endurance time.

Correlation of endurance time and maximal oxygen uptake: Because of the many factors other than the aerobic system that contribute to the endurance time, we prefer to leave the measurement as a time rather than using it to predict maximal $\dot{V}O_2$. The correlation studies shown in the results not unexpectedly indicate a high correlation between endurance time and $\dot{V}O_2$ max, but the standard error of predicting $\dot{V}O_2$ max is at least 10 percent of the mean, and nothing is gained by this extrapolation of the data.

Oxygen uptake could have been measured in every child, but our unpublished experiences with children indicate that such measurements would have reduced the endurance time in many of the younger children and lost the cooperation of several to the degree that a maximal effort would not have been made. This problem could possibly be overcome by repeated tests, but the extra time involved places direct $\dot{V}O_2$ measurements in the research laboratory and not for routine clinical use, unless it can be shown that the additional information is of clinical value.

Reproducibility tests indicated that children did not perform better on a second test. Because the test was to be used as a screening test for exercise capacity, it was desirable that no practice be necessary to perform well. The first two stages of the test were usually sufficient to eliminate any element of fear and to allow the subject to gain confidence.

Selection of normal test subjects: Lavallee et al.[10] recently reported that in a group of 700 schoolchildren followed up for 5 years, growth and $\dot{V}O_2$ max (directly measured during bicycle exercise) were the same in the 20 percent recorded to have innocent murmurs as in the 80 percent without a recorded murmur. Although this evidence supports the view that children with innocent murmurs can be considered normal subjects in stress testing, the clinic patients in our study were a special subsample of a large population of children with murmurs who happened to be referred to a specialty clinic.

Going into the schools for normative data in children permits one to collect a large sample in a short time and to use random selection methods. However, utilizing volunteers in a school environment is different from testing an often reluctant child persuaded by the parent to come to an unfamiliar hospital clinic. Both "normal" and abnormal subjects in a clinic are tested in random order as they come. The same technicians test normal subjects and patients on the same apparatus in the same environment over the same time period. When a new technician enters the system, data for normal subjects continue to be obtained. Technicians have tended to obtain a longer endurance time in the normal children as they gained experience and provided the children with greater goals. This emphasizes the need for all exercise laboratories to continue monitoring normal subjects concomitantly with test patients. Although it is possible that higher values for maximal performance may be obtained with volunteers from the school system, it is debatable whether the latter are an ideal population against which to compare clinic patients.

Advantages of method for clinical testing: The Bruce test proved to be highly suitable for the clinical exercise testing of children aged 4 years and older. The same protocol is used for all ages, the response to submaximal exercise loads may be documented, the heart rate responses are similar for children of all ages, maximal oxygen uptake can be roughly estimated, a maximal exercise capacity measurement is obtained based on what the subject actually did and not on a prediction made by extrapolation, longitudinal data on growing children can be obtained using exactly the same exercise protocol and in contrast to the bicycle ergometer, there are no calibration problems with the exercise apparatus and no need to have a large number of work loads based on body weight. No prior experience or practice by the patient is necessary and, because the belt speed is slow, injury and fear of performing on the treadmill are minor issues.

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Surgical Significance of the Coronary Arterial Anatomy in Truncus Arteriosus Communis

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In truncus arteriosus communis, as in other anomalies of conotruncal development, the coronary arterial anatomy not only differs from that found in the normal heart but also is subject to unpredictable variations. A consistently distinctive pattern was found in roughly two thirds of 31 cases, a frequency approximating that with which a distinctive coronary arterial pattern occurs in complete transposition of the great vessels. Surgical injury to a major coronary artery was identified in 2 of the 30 hearts from patients with truncus arteriosus communis who died in the early postoperative period. Of particular significance are large branches of the right coronary artery crossing the upper anterior surface of the right ventricle to supply the anterobasal surface of both ventricles and the upper part of the interventricular septum. These arteries are at special risk in surgical procedures utilizing a conduit anastomosed to a right ventriculotomy.

Truncus arteriosus communis is a congenital cardiac malformation in which a single arterial trunk arises from the heart and receives the outflow from both ventricles. There may be some inequality of positioning of the trunk so that it favors either the left or the right ventricle, and an interventricular communication is present directly beneath the single semilunar valve of the truncus. The coronary arteries arise from the truncus proximally and the pulmonary arteries arise more distally. Truncus arteriosus communis is classified by the nature of the pulmonary arterial origin from the truncus.[1,2]

This study reviews the anatomy of the coronary arteries in 31 hearts with truncus arteriosus communis and documents instances of surgical injuries to major coronary arteries that had occurred in the hearts of 30 patients who died in the early postoperative period.

Materials and Methods

Thirty-four hearts with classic truncus arteriosus communis were available for study. All the hearts were from the tissue registry of the Department of Pathology and Anatomy at the Mayo Clinic and were from autopsies performed during the 8 year period from 1968 to 1976, inclusive. The age of the patients at autopsy ranged from 18 days to 14 years. The surgical experience from this institution has previously been reported.[3] A detailed examination was made to confirm the diagnosis anatomically. The coronary ostia were examined and their position in relation to the cusps of the truncal valve was recorded. The procedure included measurements to ascertain the height of the ostia above the truncal valve ring. In three hearts, truncal valve replacement had been carried out and it was not possible to document the position of the ostia in relation to the cusps of the truncal valve. These three hearts were excluded from the component of the study dealing with the coronary arterial anatomy although they were included in the study to identify surgical injury to the more distal vessels. Careful dissection of the coronary arteries was performed and the coronary anatomy documented. A note was made of the approximate relative size of the vessels. Particular attention was paid to any areas where arteries were in close proximity to suture lines or hematoma and the lumen of the vessel in such areas was carefully examined for the presence of any occlusive lesion.

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Results

Truncal valve: To be able to document the sites of origin of the coronary arteries one must first document and establish a nomenclature for the cusps and commissures of the truncal valve. In the absence of a second semilunar valve other reference planes such as the ventricular septum and the position of origin of the pulmonary arteries must be used. It was found that if the valve was tricuspid (24 hearts [78 percent]) one commissure was pointed either anteriorly or in a right anterior oblique direction. Although there was variable rotation between these extremes, and there was often minor variation in the relative size of the individual cusps, one cusp was predominantly posterior in position. This cusp can be designated posterior and the other cusps right anterior and left anterior. If the valve is bicuspid (four hearts [13 percent]) or quadricuspid (three hearts [9 percent]), there is considerable variation in the inclination of the commissures and the position of the cusps.

Ostia and proximal coronary arteries: Thirty-one hearts were used in this component of the study. The positions of the ostia and the proximal arteries are summarized diagrammatically in Figures 1 to 3. In 19 of the 31 hearts (61 percent), regardless of whether the truncal valve was bicuspid, tricuspid or quadricuspid, the left coronary artery arose from the left posterior aspect of the truncus and the right coronary artery arose from the right anterior aspect. Thus, in 61 percent of the hearts a consistent pattern of origin of the coronary arteries was observed. A total of 4 of the 31 hearts (13 percent) had either a single ostium or very closely associated ostia.

When the truncal valve was tricuspid, the most frequent pattern (observed in 15 hearts [48 percent]) was origin of the right coronary artery from the sinus of Valsalva above the right anterior cusp so that the vessel gained very direct access to the right atrioventricular (A-V) groove. The left coronary artery arose from the sinus of Valsalva above the posterior cusp, coursed around the left side of the truncus and divided anterior to the truncus so that the mainstem of the left coronary artery was long. The left circumflex branch gained access to the left A-V sulcus but the left anterior descending branch originated well to the left. In a further four hearts (13 percent), the right coronary artery originated posteriorly and the left coronary artery from the left anterior sinus of Valsalva. This minor variation could be the result of differences in rotation of the truncus.

In five hearts the truncal valve was tricuspid but the coronary arterial anatomy was atypical (Fig. 2, A and B). In two of these hearts there were two coronary ostia, and in three hearts both arteries arose from a single ostium. In the hearts with two ostia, it was not possible to attribute the variation to differing rotation of the truncus.

In seven hearts, the truncal valve was either bicuspid (four hearts) or quadricuspid (three hearts). In the four hearts with a bicuspid valve (Fig. 3) the coronary arterial pattern and the position of the ostia approximately conformed to the positions most frequently seen with a tricuspid valve. The three hearts with a quadricuspid valve had an atypical coronary pattern, and one of these hearts had a single coronary ostium.

TABLE I
Summary of Surgical Procedures in 30 Cases of Truncus Arteriosus Communis

Procedure	Cases (no.)
Total correction utilizing a conduit	
Aortic homograft	16
Hancock conduit prosthesis	11
Palliative procedures	
Blalock-Hanlon	1
Pulmonary arterial banding	1
Exploration only	1
Total	30

Anterior surface of the right ventricle: This area is of considerable importance because it is here that ventriculotomy incisions are made and conduit prostheses are anastomosed during reparative surgical procedures. As previously mentioned, in the most frequently observed coronary arterial pattern the left coronary artery bifurcated well to the left of the truncus. Thus, at its origin it was displaced to the left of the interventricular sulcus. It then coursed downward on the surface of the left ventricle, not reaching the interventricular sulcus until a point approximately halfway down the anterior surface of the heart. This pattern was previously described by Bharati et al.[4] Furthermore, the vessel was usually smaller in caliber than one expects the left anterior descending coronary artery to be. The small size and the leftward displacement of this vessel appear to result in a greatly reduced contribution to the blood supply of the right ventricle and the interventricular septum. Large diagonal branches of the right coronary artery, which run a course parallel to the conus artery but are situated farther down on the anterior surface of the right ventricle, are almost invariably present in truncus arteriosus communis (Fig. 4). The conus artery and these other diagonal branches of the right coronary artery supply almost all the anterior surface of the right ventricle, often the upper interventricular septum and occasionally part of the anterior surface of the left ventricle.

Surgical injury to the coronary arteries: In the 34 cases available, 30 patients had recent surgical procedures (Table I). In the majority (27 cases), the procedure utilized a conduit, either an aortic homograft or a Hancock valved conduit prosthesis. The operative procedure involved patch closure of the right ventricular outflow tract to the truncus, detachment of the pulmonary vessel or vessels from the truncus and placement of the conduit between the right ventriculotomy and detached pulmonary arteries.[5]

Injury to a major coronary artery was identified in two cases. In one, the injury involved the main right coronary artery, which had been drawn up from its position

in the right A-V sulcus and obliterated by sutures closing the right atriotomy wound in the appendage (Fig. 5). In the other, a large diagonal branch of the right coronary artery on the anterior surface of the right ventricle above the ventriculotomy was tied after inadvertent injury. As previously mentioned, large diagonal branches of the right coronary artery traversing to the left on the anterior surface of the right ventricle are frequently present in truncus arteriosus communis. In two further cases, similar arteries of moderate size were obliterated by sutures attaching the conduit to the right ventriculotomy, and in all cases some much smaller vessels were by necessity compromised. In none of the hearts in which vessels were occluded was a localized area of myocardial infarction distinguishable macroscopically or microscopically from the generalized pathologic changes usually present in patients who die in the immediate period after open heart surgery.

Discussion

In congenital anomalies of conotruncal development coronary arterial anatomy differs from that found in the normal heart and is subject to a greater likelihood of unpredictable variations. This has been well established

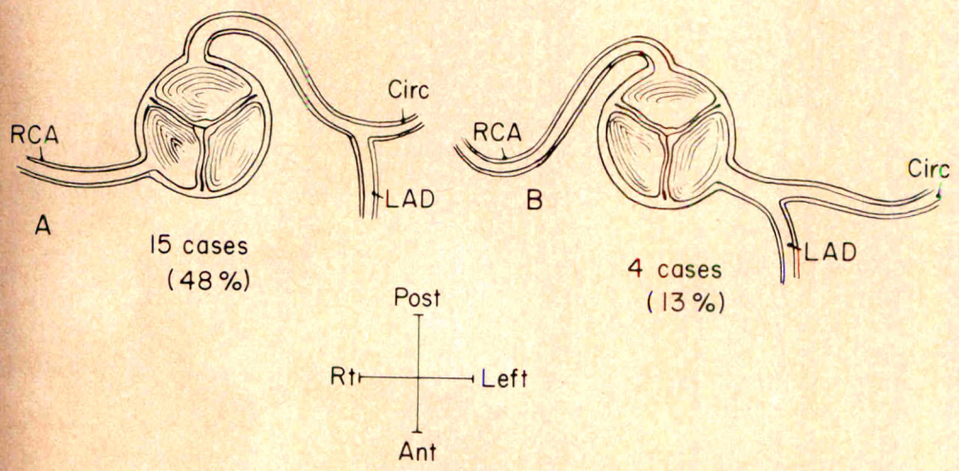

FIGURE 1. The most commonly encountered positions of the coronary arterial ostia in truncus arteriosus communis in our series. The lesser variation (**B**), present in four cases, can be explained on the basis of a variable degree of rotation of the trunk. Ant = anterior; Circ = left circumflex coronary artery; LAD = left anterior descending coronary artery; Post = posterior; RCA = right coronary artery; Rt = right.

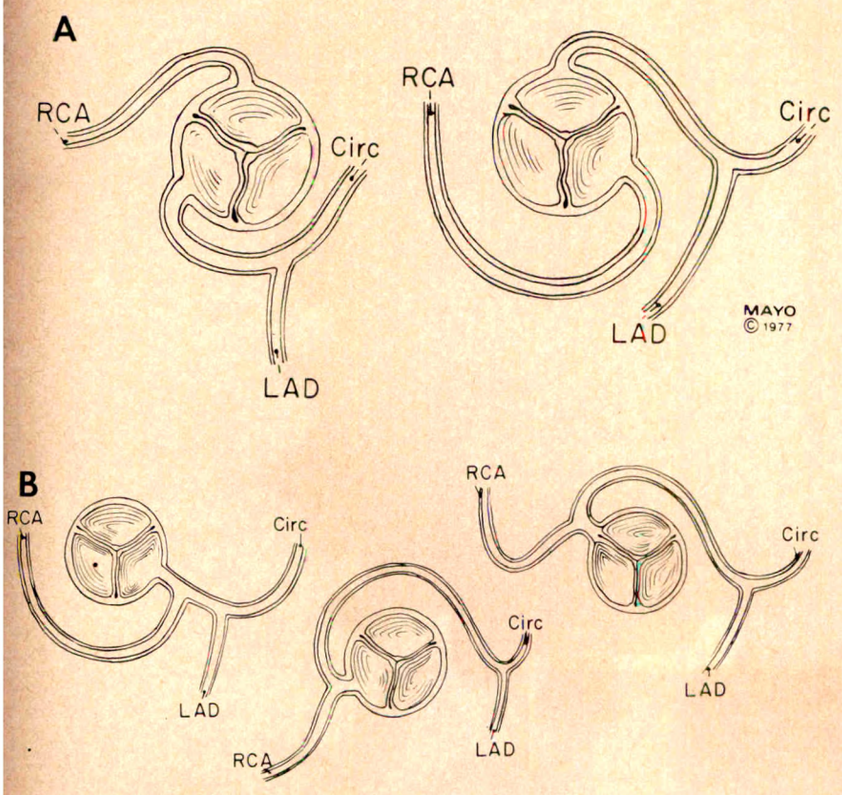

FIGURE 2. The position of the coronary ostia in five hearts with a tricuspid truncal valve but atypical coronary arterial anatomy. **A,** the two hearts with two coronary ostia; **B,** the three hearts with a single coronary ostium. Orientation and abbreviations as in Figure 1.

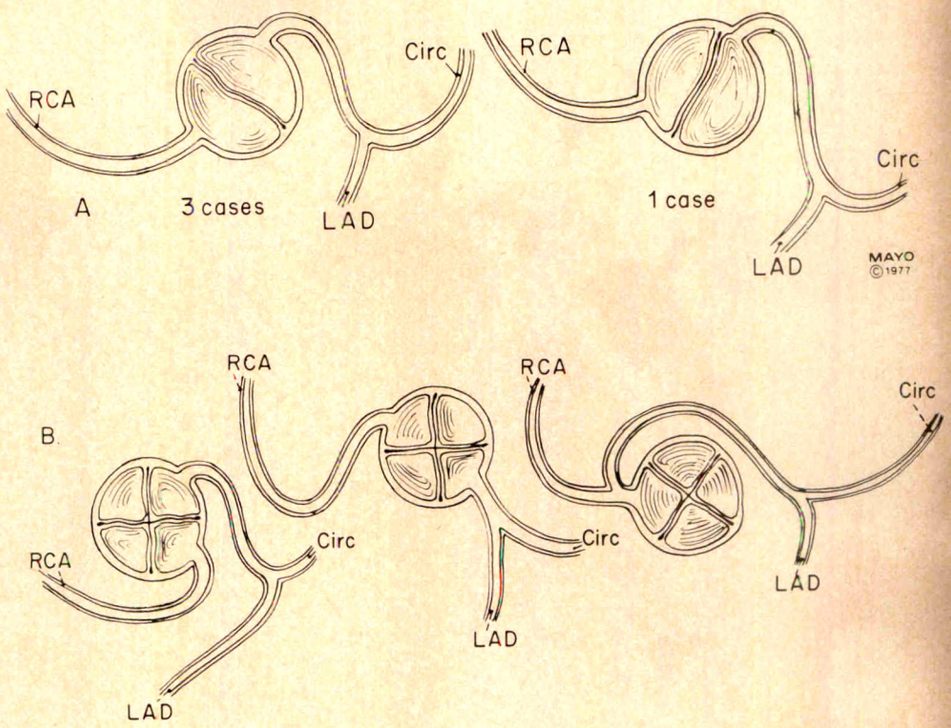

FIGURE 3. The position of the coronary ostia in seven hearts with a bicuspid or quadricuspid truncal valve. **A,** the four hearts with a bicuspid valve; **B,** the three hearts with a quadricuspid valve. Orientation and abbreviations as in Figure 1.

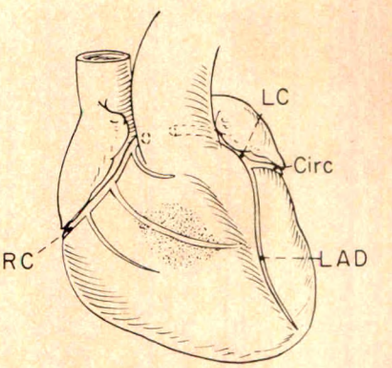

FIGURE 4. Diagrammatic illustration of the anterior surface of a heart with truncus arteriosus communis showing the coronary arterial anatomy often encountered. The anterior descending branch (LAD) of the left coronary artery (LC) is displaced to the left in its proximal course and does not reach the anterior interventricular sulcus till a point approximately halfway down the anterior surface of the ventricles. Large diagonal branches of the right coronary artery (RC) running parallel to the conus artery but situated farther down on the surface of the right ventricle are usually present. These arteries are in danger of being injured by a ventriculotomy incision or when a conduit is anastomosed to the right ventricle (**stippled area**). Circ = circumflex branch of the left coronary artery.

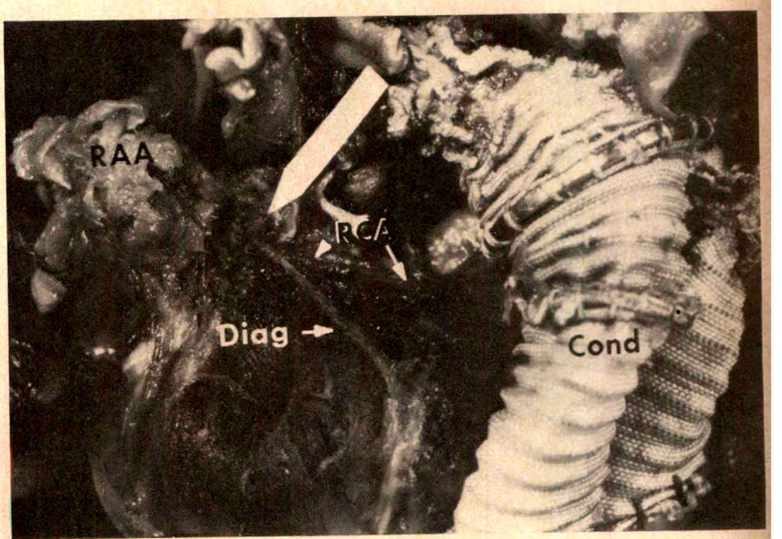

FIGURE 5. Surgical injury to the right coronary artery (RCA), which has been drawn up from its position in the right A-V groove (**arrow**) and incorporated in sutures securing the atriotomy wound in the right atrial appendage (RAA). Cond = conduit prosthesis (right ventricle to pulmonary artery); Diag = diagonal branch of the right coronary artery.

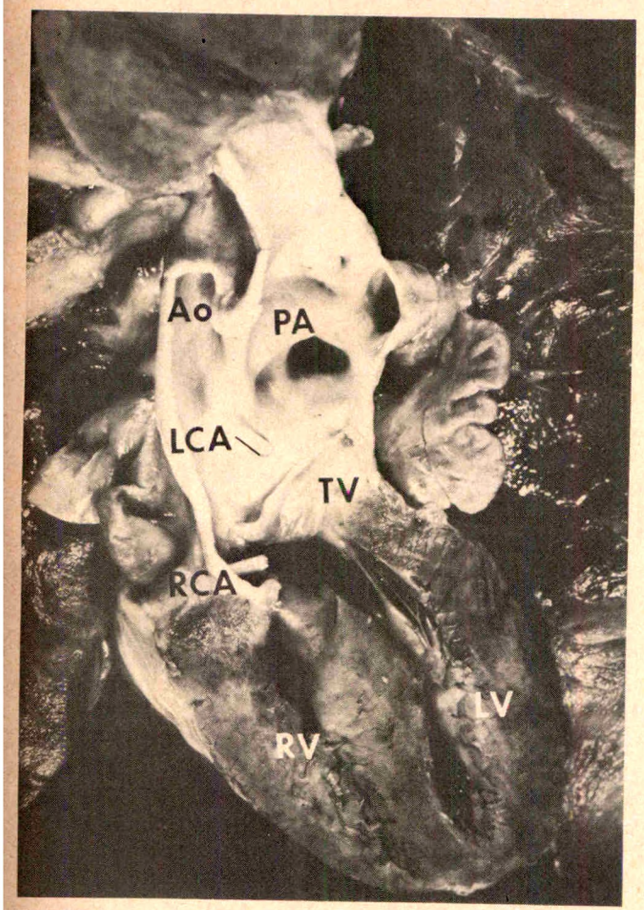

FIGURE 6. Heart at autopsy showing the truncus and truncal valve (TV) opened to expose the coronary ostia. The left coronary arterial ostium is anomalously high above the sinus of Valsalva and in close proximity to the origin of the pulmonary artery. Ao = aorta; LCA = left coronary artery; LV = left ventricle; PA = pulmonary artery; RCA = right coronary artery; RV = right ventricle; TV = truncal valve.

in complete transposition of the great vessels,[6–8] and appears to apply also to truncus arteriosus communis.[9] In explaining the embryologic basis of transposition, the abnormal positions of the coronary ostia are part of the evidence favoring a hypothesis involving disordered conotruncal rotation rather than deficient spiraling of the aorticopulmonary, truncal and conal septa. Truncus arteriosus communis is generally believed to be the result of failure of growth of these septa but it seems probable that a rotational anomaly of the truncus must also occur to explain the displacement of the ostia.

Previous mention has been made of the abnormally high position of the coronary ostia in truncus arteriosus communis.[4,10] In some of our cases an ostium was noted to arise at or slightly above the junction of the sinus of Valsalva to the ascending truncus, but we did not consider this a significant anomaly when measurements from the aortic valve ring were considered. The junction of the sinus to the ascending truncus is often variable and difficult to define. Although not in this series, we have observed a very high anomalous left ostium situated just below the origin of the pulmonary trunk (Fig. 6). Such an artery would have been in danger when the pulmonary trunk was divided from the truncus during a total correction procedure, but we believe that anomalously high ostia of this degree are uncommon in truncus arteriosus communis.

Surgical implications: The two patients whose major coronary arteries were ligated and the two whose smaller anterior diagonal branches were injured died in the immediate postoperative period. Low output failure and arrhythmias were the cause of death. There appeared to be no features to distinguish the low output failure in these cases from low output failure of other causes occurring after cardiac surgery. Although it is only speculative that these injuries were responsible for the postoperative heart failure and arrhythmias, it is likely that they contributed significantly. In two cases injuries were to major vessels: in one case to the main right coronary and in the other to an anterior diagonal branch of the right coronary artery, which was similar in caliber to the left anterior descending artery. Patients in the pediatric age group usually do not have coronary artery disease and therefore would not be expected to have significant collateral vessels. Thus, occlusion of a major coronary artery would be expected to lead inevitably to infarction. Infarction at this time when cardiac function is already compromised as a result of surgery might well be expected to have disastrous consequences. Myocardial infarction was not identified, either macroscopically or with routine light microscopy, in the two hearts in which major coronary arteries were occluded. This is not surprising because the patients in both cases died in the early postoperative period after cardiopulmonary bypass, and the changes in the myocardium attributable to open heart surgery and subsequent resuscitation efforts would obscure the subtle pathologic changes of very recent myocardial infarction.

Anterior diagonal branches of the right coronary artery are almost invariably present in truncus arteriosus communis. Their course approximately parallels that of the conus artery except that they are situated lower down on the anterior wall of the ventricle. The importance of these vessels is enhanced because the left anterior descending coronary artery is often small and tends to be displaced well to the left in its proximal course. Thus, these branches of the right coronary artery supply the anterior surface of the right ventricle and may supply a significant proportion of the upper anterior wall of the left ventricle. It is also probable that they give rise in some cases to the perforating branches to the upper interventricular septum.

Clinical implications: We have demonstrated that anterior diagonal branches of the right coronary may be divided by a ventriculotomy incision or may be obliterated by sutures securing a conduit anastomosed to the ventriculotomy. This risk is greatly accentuated when the coronary arteries cannot be visualized at surgery because of pericardial fibrosis resulting from previous operative procedures. Special care and preoperative documentation of the coronary arteries, particularly the right coronary artery, with selective coronary angiography may be indicated in these cases.

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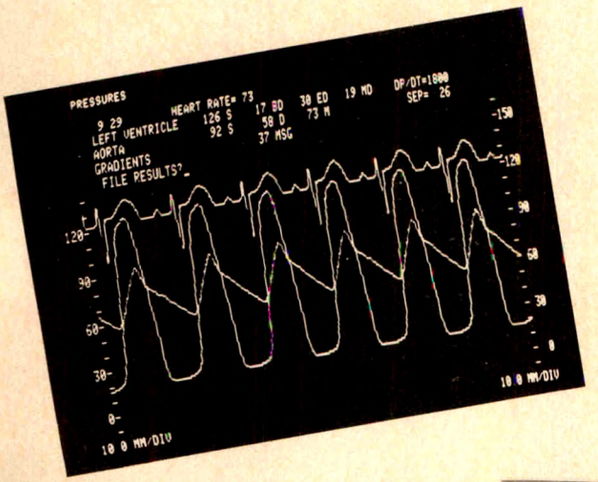

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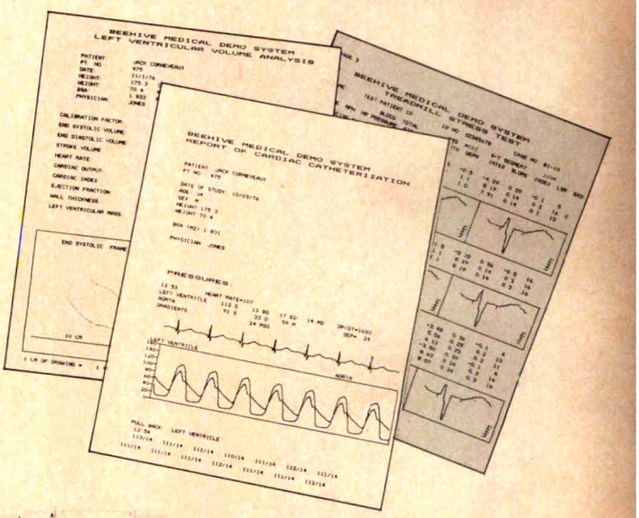

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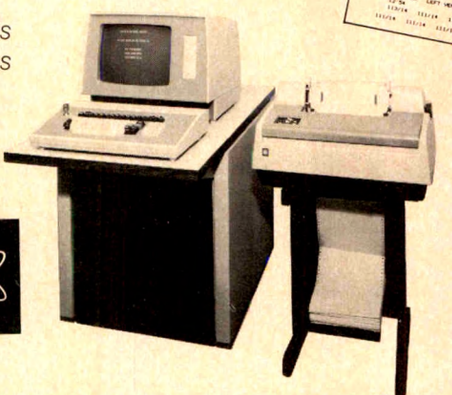

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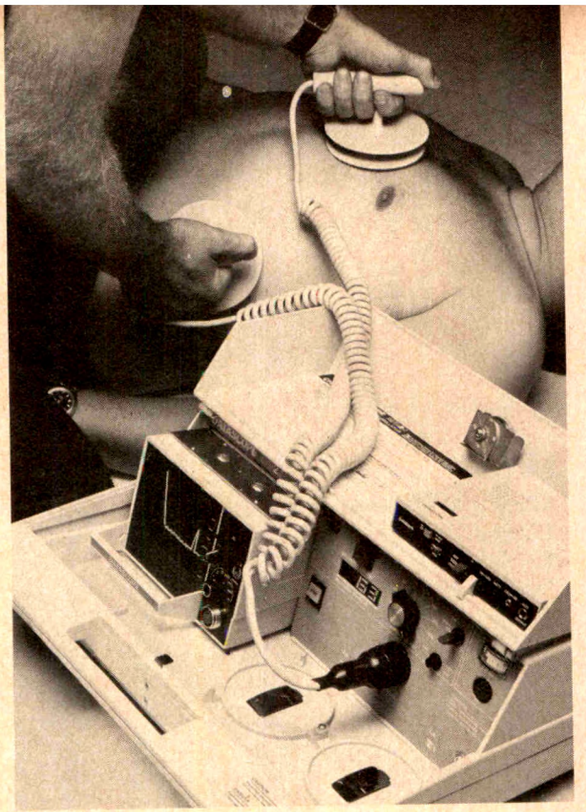

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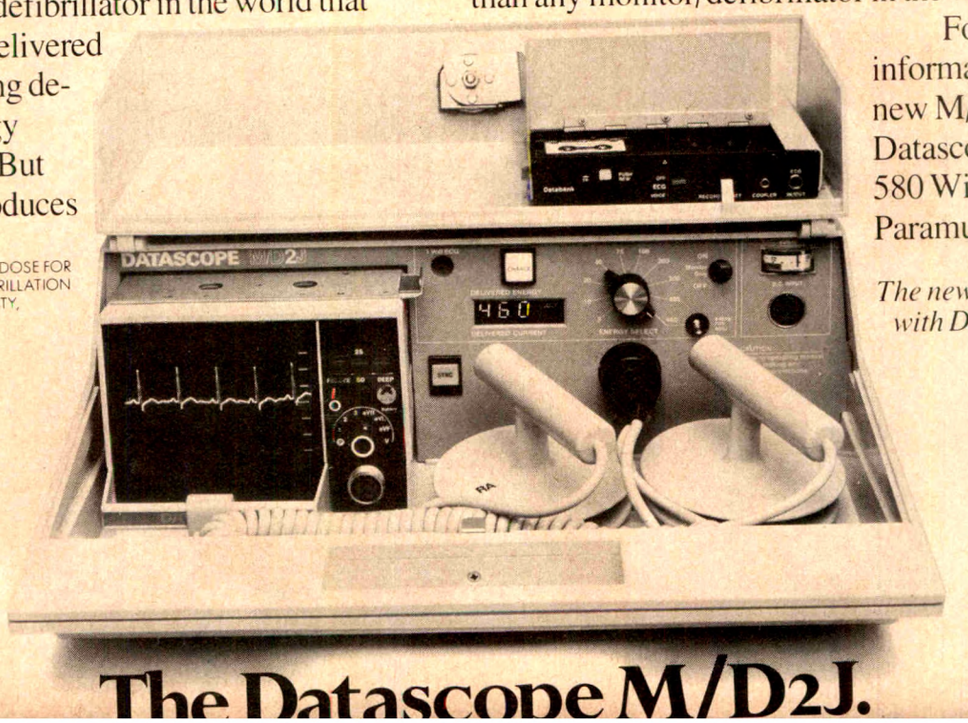

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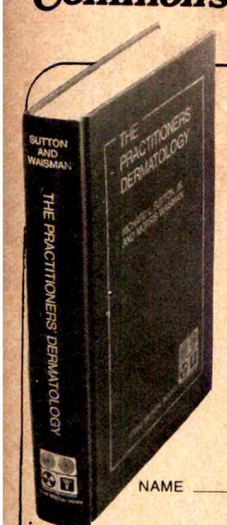

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Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:
(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).

Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).

Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

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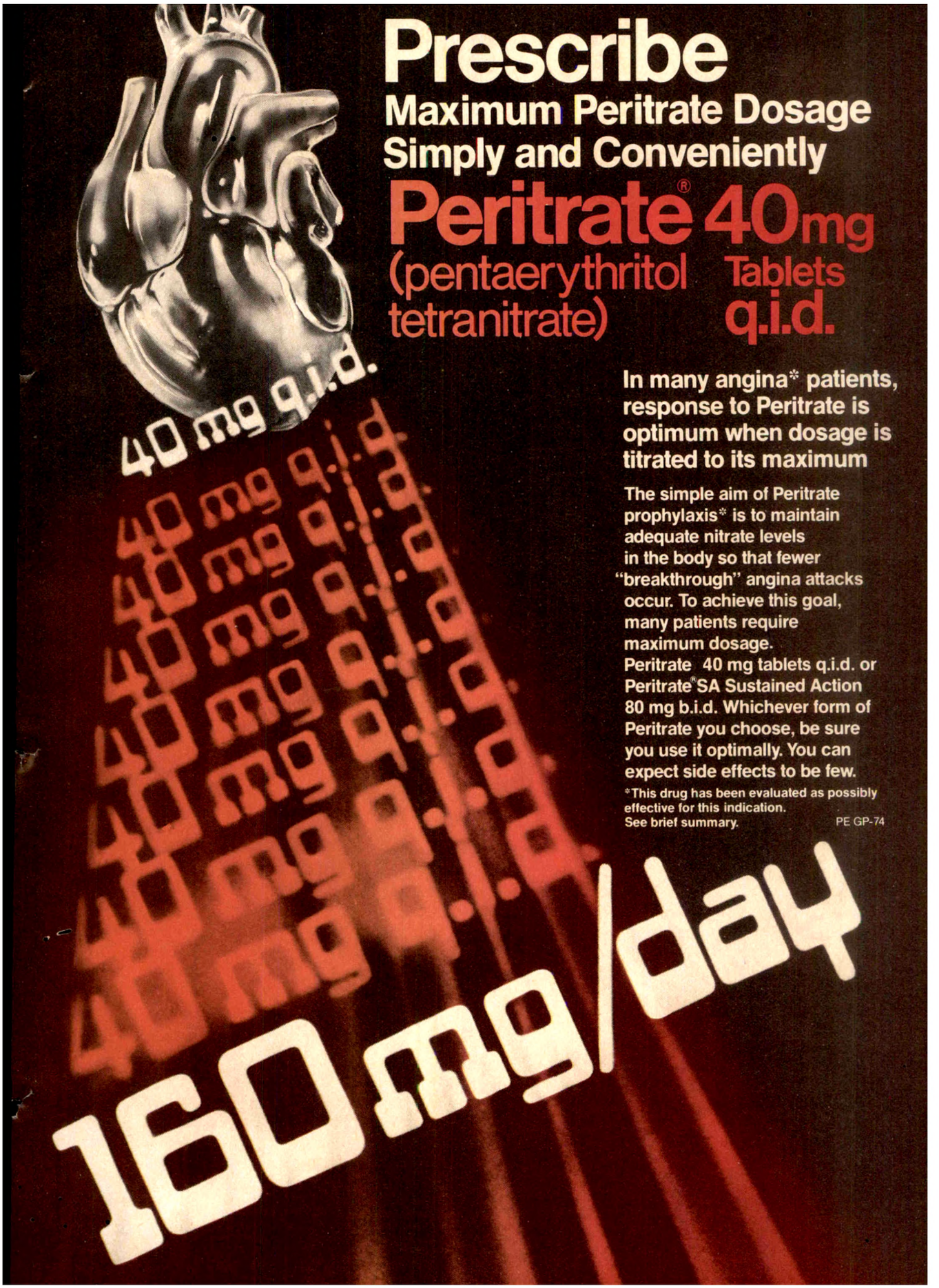
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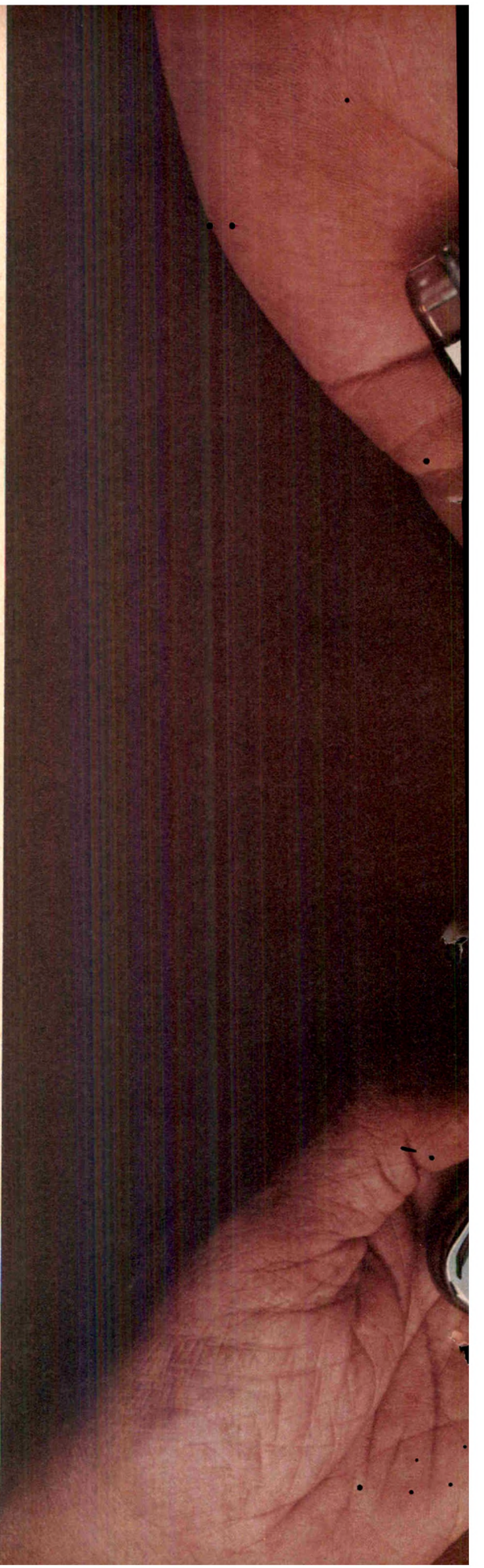

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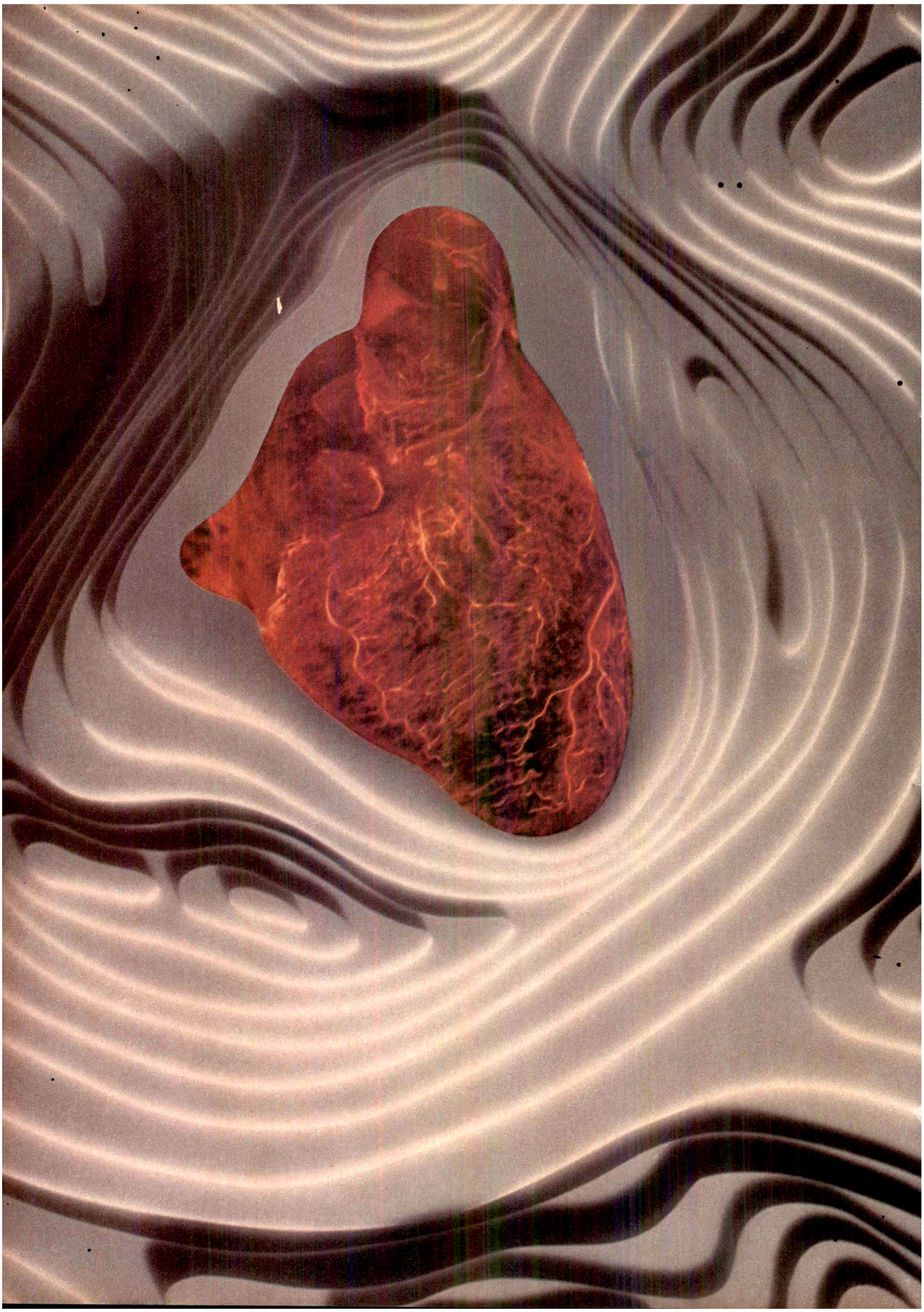

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* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: Possibly effective: For the management, prophylaxis or treatment of anginal attacks. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, hypotension, increased intracranial pressure and idiosyncrasy to this drug.

Warnings: For ORAL, not sublingual use. Capsules must be swallowed whole. NITRO-BID® 2.5 and 6.5 Capsules are not intended for immediate relief of anginal attacks.

Precautions: Use the smallest dose which proves effective because continued administration of larger doses may lead to tolerance. Intraocular pressure may be increased; therefore, caution is required in administering to patients with glaucoma. If blurring of vision or dryness of mouth occurs, drug should be discontinued.

Adverse Reactions: Occasionally transient headaches may occur. Overdoses may cause flushing, headaches, tachycardia, dizziness.

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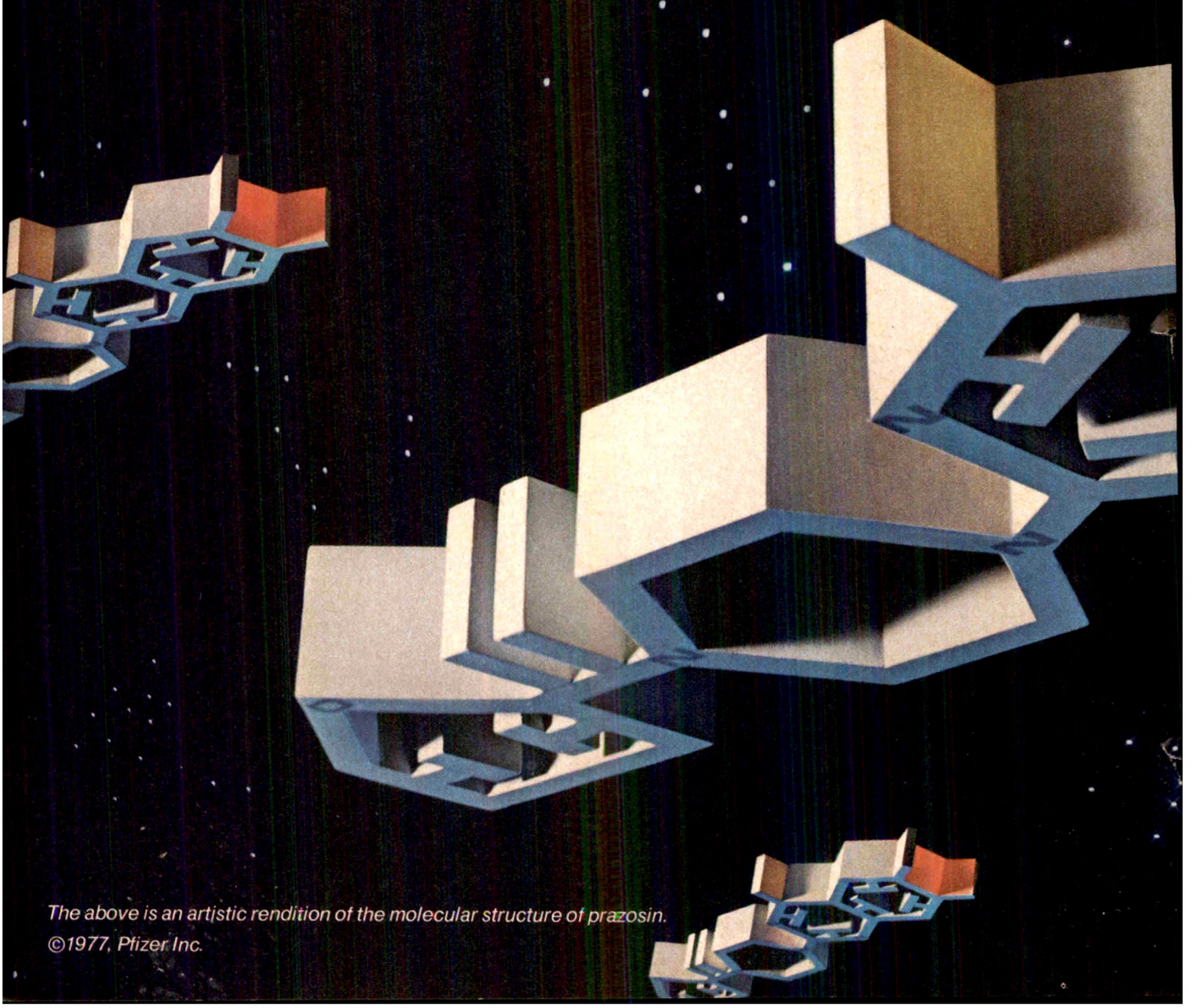

The above is an artistic rendition of the molecular structure of prazosin.

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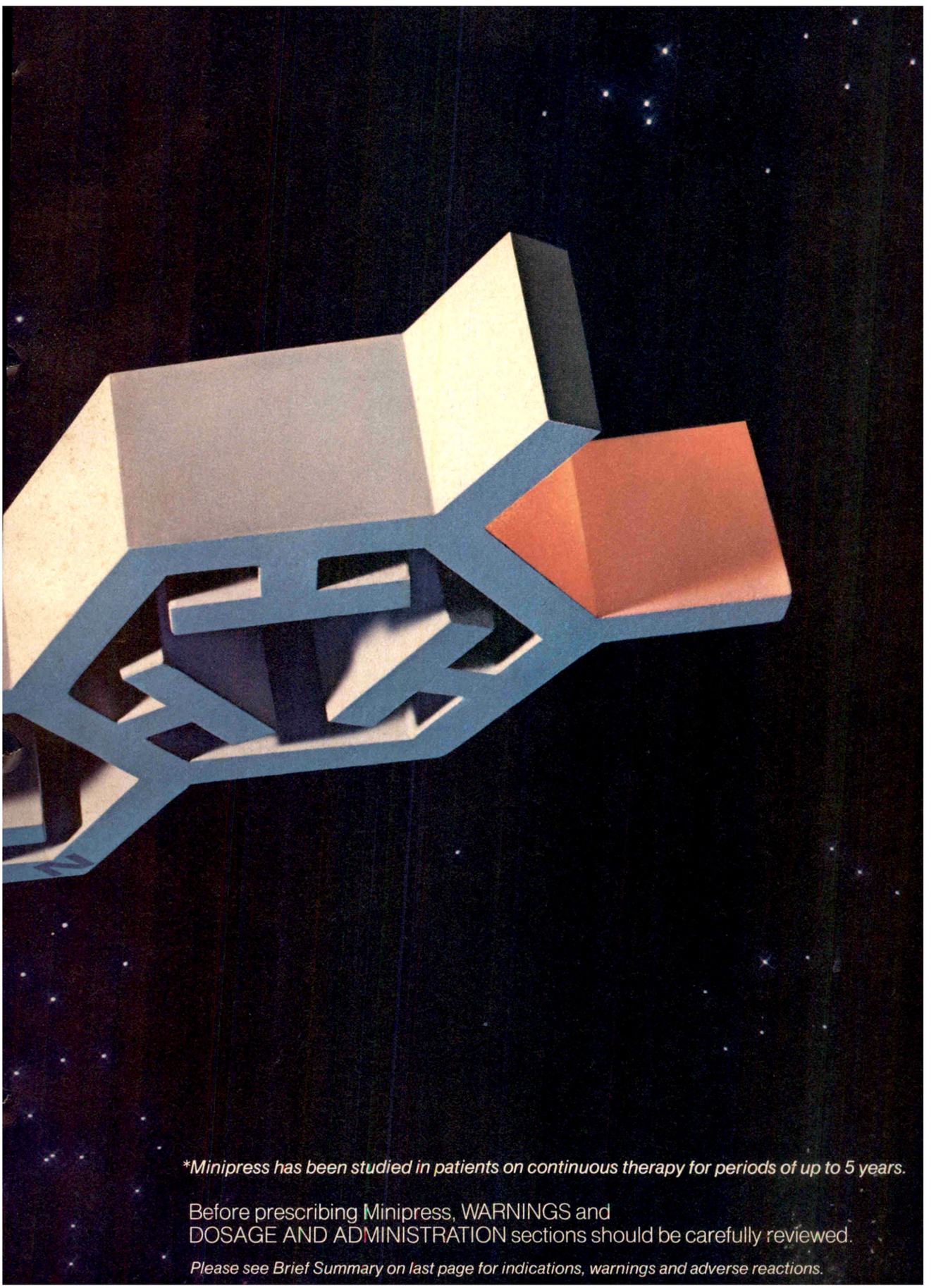
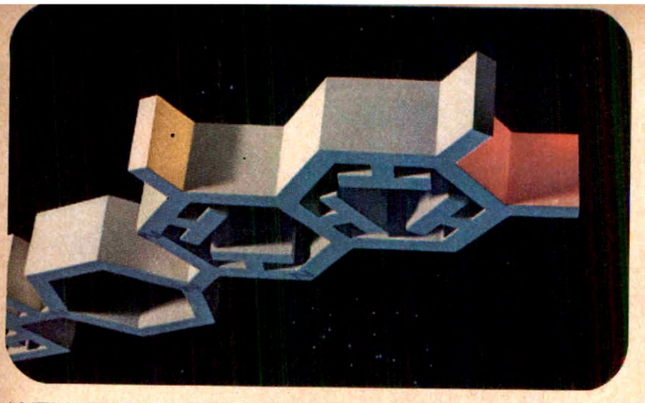


**Minipress has been studied in patients on continuous therapy for periods of up to 5 years.*

Before prescribing Minipress, WARNINGS and DOSAGE AND ADMINISTRATION sections should be carefully reviewed.

Please see Brief Summary on last page for indications, warnings and adverse reactions.



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- Direct action on the arterioles without clinically significant effects on cardiac output, renal blood flow or glomerular filtration rate. Reflex tachycardia frequently associated with other vasodilators is much less common with Minipress.
- No tolerance observed in long-term therapy in patients on continuous therapy for periods of up to 5 years.
- Studies in patients on continuous therapy for periods of up to 5 years indicate that Minipress is well suited for long-term therapy.
- Side effects most frequently experienced with Minipress in a series of 934 patients were: dizziness (10.3%), headache (7.8%), drowsiness (7.6%), lack of energy (6.9%), weakness (6.5%), palpitations (5.3%), and nausea (4.9%). A small percentage of patients have experienced orthostatic hypotension (3.4%) and syncope (1.3%). (For a more detailed description of orthostatic hypotension and syncope, see Warnings in Brief Summary before initiating therapy with Minipress.)
- Starting dosage: 1 mg t.i.d.
- Usual maximum recommended dosage: 20 mg daily, given in divided doses.
- Some patients can be maintained adequately on a b.i.d. dosage regimen.
- Available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit dose packages of 100 (10 x 10's).

More detailed information available on request.

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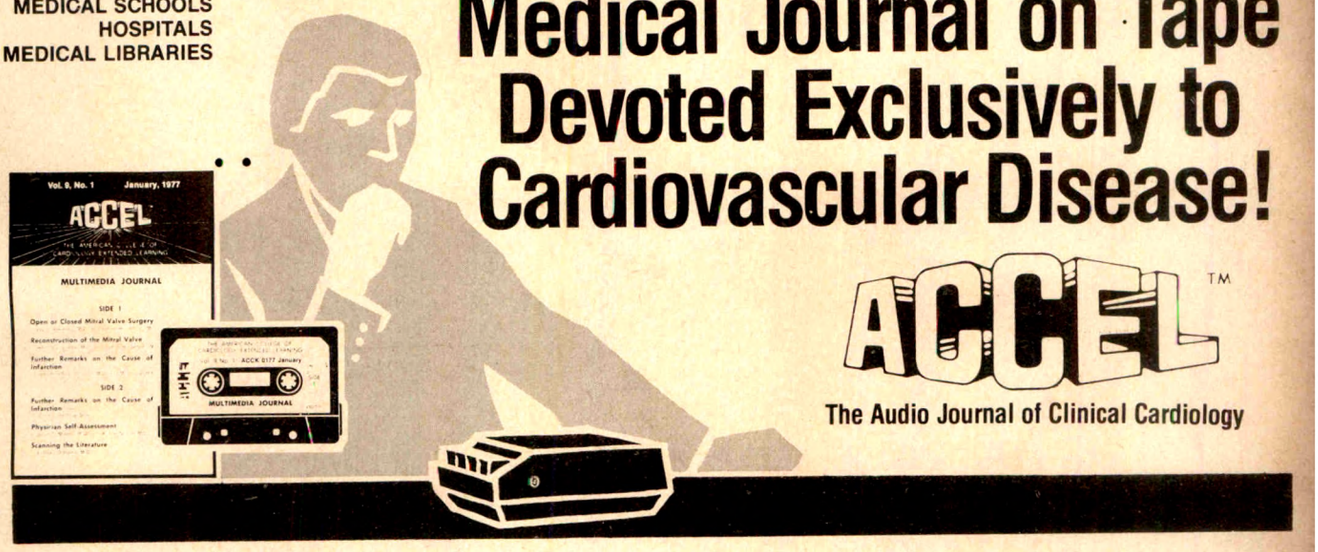

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Effects of Long-Term Oral Administration of Isosorbide Dinitrate On the Antianginal Response to Nitroglycerin

Absence of Nitrate Cross-Tolerance and Self-Tolerance Shown by Exercise Testing

GARRETT LEE, MD
DEAN T. MASON, MD, FACC
ANTHONY N. De MARIA, MD, FACC*

Davis and Sacramento, California

Controversy exists regarding the ability of sustained-release orally administered nitrates to induce cross-tolerance to sublingual doses of nitroglycerin. Therefore this study compared the effects of isosorbide dinitrate and placebo on nitroglycerin-induced improvement in exercise testing in 28 patients with coronary artery disease. Maximal exercise tests were performed in all patients before and 10 minutes after sublingual administration of 0.6 mg of nitroglycerin both before and after 1 month of administration of either placebo or isosorbide. During the control period, nitroglycerin produced improvement in mean duration of exercise (placebo from 302 to 390 seconds and isosorbide from 302 to 391 seconds; both $P < 0.001$) and a derived index of maximal oxygen consumption (placebo from 21.1 to 24.5 and isosorbide from 21.1 to 24.8 cc/kg per min; both $P < 0.001$); maximal heart rate-blood pressure product remained unchanged (placebo from 23.3 to 23.7 $\times$ 10^3 and isosorbide from 19.2 to 20.2 $\times$ 10^3; both $P > 0.05$). During the posttreatment period nitroglycerin again resulted in increases in exercise duration (placebo from 306 to 368 seconds and isosorbide from 373 to 411 seconds; both $P < 0.01$) and a derived index of oxygen consumption (placebo from 21.3 to 23.7 and 23.9 to 25.4 cc/kg per min; both $P < 0.01$) whereas maximal heart rate-blood pressure product was without change with placebo ($P > 0.05$) but minimally higher after administration of isosorbide (20.7 to 22.8 $\times$ 10^3; $P < 0.01$). An identical level of S-T segment improvement was achieved at maximal exertion after nitroglycerin in both groups. Thus the demonstration in this study of the ability to achieve equivalent improvements in exercise performance before and 1 month after isosorbide dinitrate therapy indicates that long-term oral administration of large doses of this long-acting nitrate does not result in cross-tolerance to the antianginal action of sublingually administered nitroglycerin. In addition, the long-acting nitrate achieved therapeutic efficiency without evidence of self-tolerance.

From the Section of Cardiovascular Medicine, Departments of Medicine and Physiology, University of California at Davis, School of Medicine, Davis, California and Sacramento Medical Center, Sacramento, California. This study was supported in part by Research Program Project Grant HL-14780 from the National Heart, Lung, and Blood Institute; National Institutes of Health, Bethesda, Maryland. Manuscript received April 5, 1977; revised manuscript received June 27, 1977, accepted June 29, 1977.

* Present address and address for reprints: Anthony N. DeMaria, MD, Sacramento Medical Center, 2315 Stockton Blvd., Sacramento, California 95817.

Although nitroglycerin given sublingually has long been demonstrated to be an effective antianginal agent, considerable controversy has existed regarding the value of sustained-release orally administered nitrate preparations in the treatment of angina pectoris.[1–4] Indeed, initial experimental studies[5] regarding the absorption and metabolism of ingested nitroglycerin indicated that the agent underwent complete biotransformation by the liver to inactive metabolites and thus could not be administered by the oral route. Recently, however, numerous studies[6–8] have demonstrated the ability of orally administered isosorbide dinitrate, when administered in large doses, to induce beneficial effects in patients with coronary artery disease. Thus, alleviation of symptoms,[6,9] enhanced exercise tolerance,[7,8,10,11] reduced electrocardiographic manifestations of myocardial ischemia[6–8] and favorable alterations in cardiocirculatory

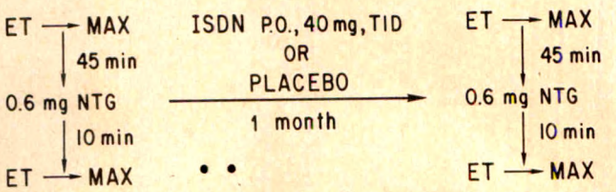

FIGURE 1. Summary of the study protocol. ET = exercise test; ISDN = isosorbide dinitrate; MAX = maximal symptom-limited exertion; min = minutes; NTG = nitroglycerin; P.O. = orally; TID = three times daily.

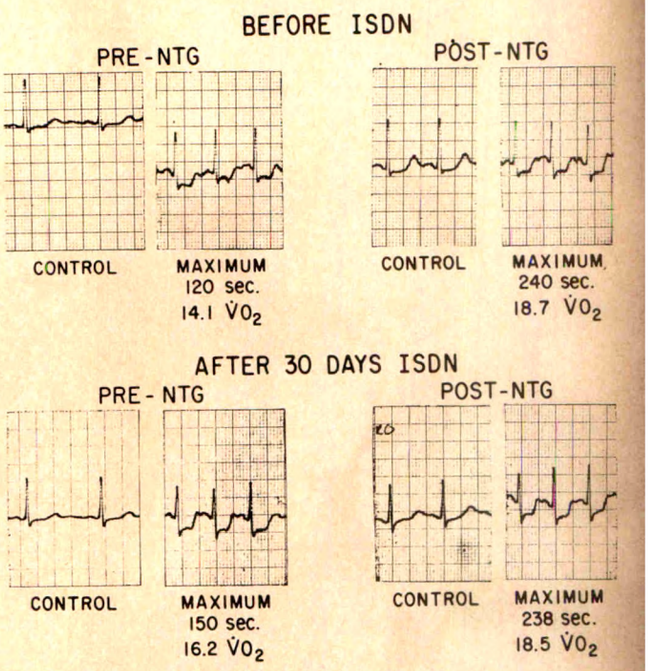

FIGURE 2. Exercise electrocardiograms pre- and postsublingual administration of nitroglycerin (NTG) before and after 1 month of isosorbide dinitrate (ISDN). $\dot{V}O_2$ = a derived index of oxygen consumption.

hemodynamics[4,12–14] have all been documented to occur after the oral administration of isosorbide dinitrate. Accordingly, the sustained-release orally administered preparation of this organic nitrate is being widely applied in the prophylactic treatment of angina pectoris.

Although considerable data are available regarding the antianginal effects of isosorbide dinitrate, the ability of this agent to induce cross-tolerance to sublingually administered nitroglycerin remains unresolved. Thus, some investigators[15,16] have reported attenuation of the acute nitroglycerin-induced changes in heart rate, blood pressure and venous tone after long-term treatment with long-acting nitrates, but such findings have not been universal.[17] Further, no data are available regarding the relation of such decreases in circulatory responsiveness and the clinical antianginal action of sublingual doses of nitroglycerin. Exercise stress testing provides a method of objectively assessing the clinical effect of sublingually administered nitroglycerin on angina pectoris. In this study we utilized such testing to evaluate whether prolonged oral administration of sustained-release isosorbide dinitrate would induce cross-tolerance to the antianginal effect of sublingual doses of nitroglycerin.

Methods

Patients: Twenty-eight patients (20 men and 8 women, mean age 56 years) with atherosclerotic heart disease and stable angina pectoris were studied. The presence of coronary artery disease was documented with coronary arteriography in all 23 patients who underwent this procedure; the additional five patients manifested classic symptoms of angina pectoris or had electrocardiographic evidence of a previous myocardial infarction. No patient had demonstrated evidence of acute myocardial infarction for at least 3 months before this study, had signs or symptoms of heart valve disease or congestive heart failure or was taking digitalis, beta adrenergic blocking agents or any other coronary vasodilator other than sublingually administered nitroglycerin. All patients had previously manifested 1 mm or greater S-T segment depression on electrocardiography during treadmill exercise testing and had responded to sublingual administration of nitroglycerin with increased duration of treadmill exercise.

Exercise testing: The stress protocol utilized consisted of multistage treadmill exercise according to the method of Bruce et al.[18] Exercise was performed on a motorized treadmill (model 18-49C, Quinton Instruments, Seattle, Washington) while the electrocardiogram was obtained on a multichannel recorder (model 3500, Marquette Medical Instruments, Milwaukee, Wisconsin or model 7712, Hewlett-Packard Instruments, Palo Alto, California). Electrocardiographic leads I, aVF and V_5 were monitored continuously throughout the exercise test; a recording of these leads was obtained at 3 minute intervals and for 6 minutes after the termination of exercise. Systemic blood pressure was also measured at 3 minute intervals and at the termination of exercise by means of a cuff sphygmomanometer. All patients had prior exposure to this form of exercise testing to negate the effect of habituation on the reproducibility of exertional performance. Informed consent was obtained in every case.

Protocol (Fig. 1): At the initiation of the study, each patient underwent an exercise test performed to maximal exertion limited by the symptoms of angina, fatigue or marked dyspnea. After a 45 minute period of rest, 0.6 mg of nitroglycerin was given sublingually. After a further 10 minute period designed to ensure optimal nitroglycerin effect, the exercise test was repeated. All patients then received in double blind fashion capsules of similar appearance containing either placebo or isosorbide dinitrate, 40 mg,* each taken orally every 8 hours for 1 month. Six hours after ingestion of the last capsule, exercise tolerance before and after sublingual administration of nitroglycerin was reevaluated. Thus, the study was designed to determine whether the improvement in exercise performance induced by nitroglycerin was attenuated by the subsequent administration of the long-acting antianginal agent isosorbide dinitrate.

The following measurements were obtained in both placebo and isosorbide dinitrate–treated patients: maximal duration of exercise in seconds, a derived index of maximal total body oxygen consumption obtained from a regression equation derived by Bruce et al.[18] relating oxygen consumption to duration of exertion, heart rate-blood pressure product (which permits estimation of myocardial oxygen consumption calculated as the product of maximal heart rate and peak systolic blood pressure) and S-T segment depression in the electrocardiogram. Results were subjected to statistical analysis according to Student's *t* test for paired data.

* Kindly supplied as Isosordil Tembids® by Clarence Denton, MD, Ives Laboratories, New York, New York.

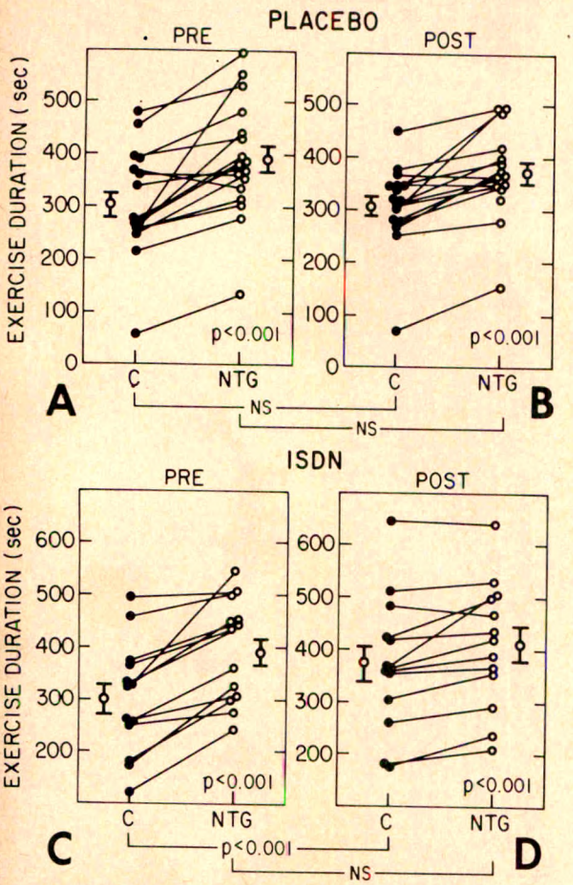

FIGURE 3. Individual, group mean and standard error of the mean data for exercise duration before (PRE) and after (POST) 1 month of treatment with placebo or isosorbide dinitrate (ISDN) capsules. Prenitroglycerin control (C) and postnitroglycerin (NTG) exercise tests were performed at each period. NS = not significant; p = probability.

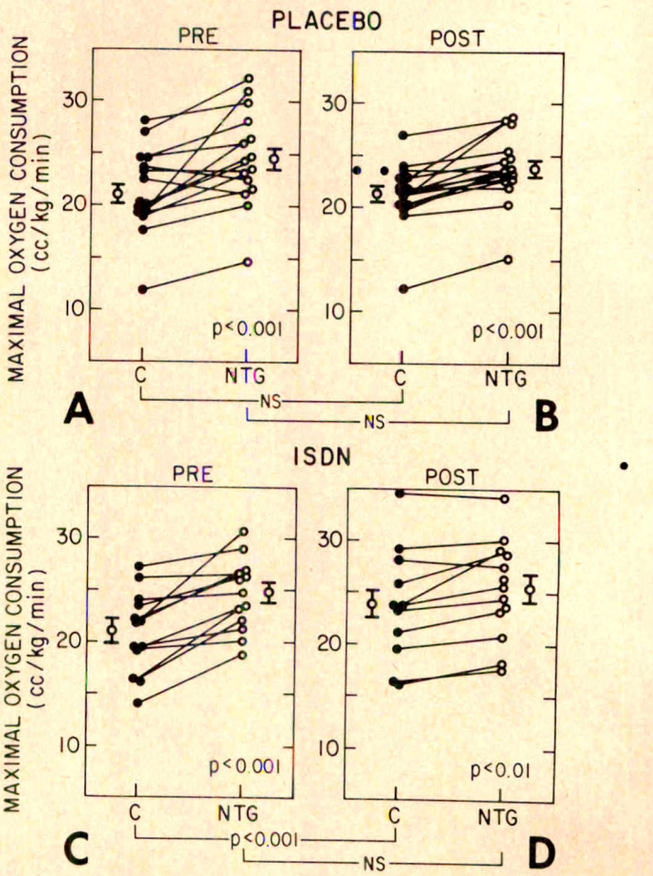

FIGURE 4. Group data for a derived index of oxygen consumption ($\dot{V}O_2$). Data presentations and abbreviations as in Figure 3.

Results

All patients manifested at least 1 mm of S-T segment depression for 60 msec on exercise electrocardiography. Figure 2 represents the electrocardiographic record from a representative patient who received isosorbide dinitrate. No significant alterations were observed in the symptoms that resulted in the termination of exercise after administration of either placebo or isosorbide dinitrate.

Duration of exercise: Individual and mean data on the duration of exercise are shown in Figure 3. During the control period in patients who received placebo (Fig. 3A), the sublingual administration of nitroglycerin prolonged the duration of exercise from 302 ± 24 to 390 ± 27 seconds (mean ± standard error of the mean) (P <0.001). One month after placebo therapy this group manifested an almost identical (P >0.05) increase in exercise duration from 306 ± 18 to 368 ± 20 seconds (P <0.001) (Fig. 3B). Thus, no significant difference was observed in the increased duration of treadmill exercise after sublingually administered nitroglycerin in the patients who received placebo. Premedication exercise tests in the patients who received isosorbide dinitrate also demonstrated an increased duration of exercise after nitroglycerin from 302 ± 30 to 391 ± 27 seconds (P <0.001) (Fig. 3C). After 1 month of isosorbide dinitrate therapy, prenitroglycerin exercise test duration in this group increased to 373 ± 36 seconds (P <0.001) (Fig. 3D), a value significantly higher than that of the prenitroglycerin exercise duration before isosorbide dinitrate therapy. Importantly, after nitroglycerin the maximal achievable duration of exertion in the group given isosorbide dinitrate was increased even further than before the sublingual administration of this agent, to 411 ± 34 seconds (P <0.001) (Fig. 3D). In addition, the maximal period of exertion after the administration of nitroglycerin was similar (P >0.05) before and after the 1 month period of isosorbide dinitrate therapy.

Maximal oxygen consumption index: Data regarding the derived index of maximal oxygen consumption are given in Figure 4. Maximal oxygen consumption improved from 21.1 ± 0.9 (prenitroglycerin) to 24.5 ± 1.0 (postnitroglycerin) (P <0.001) (Fig. 4A) and from 21.3 ± 0.7 (prenitroglycerin) to 23.7 ± 0.8 (postnitroglycerin) cc/kg per min (P <0.001) (Fig. 4B) before and after, respectively, 1 month of placebo administration. In patients who received isosorbide dinitrate the increase in derived oxygen consumption after administration of nitroglycerin was similar to that of the patients who received placebo, from 21.1 ± 1.2 to 24.8 ± 1.0 (P <0.001) (Fig. 4C) and 23.9 ± 1.4 to 25.4 ± 1.3 cc/kg per min (P <0.01) (Fig. 4D) before and after, re-

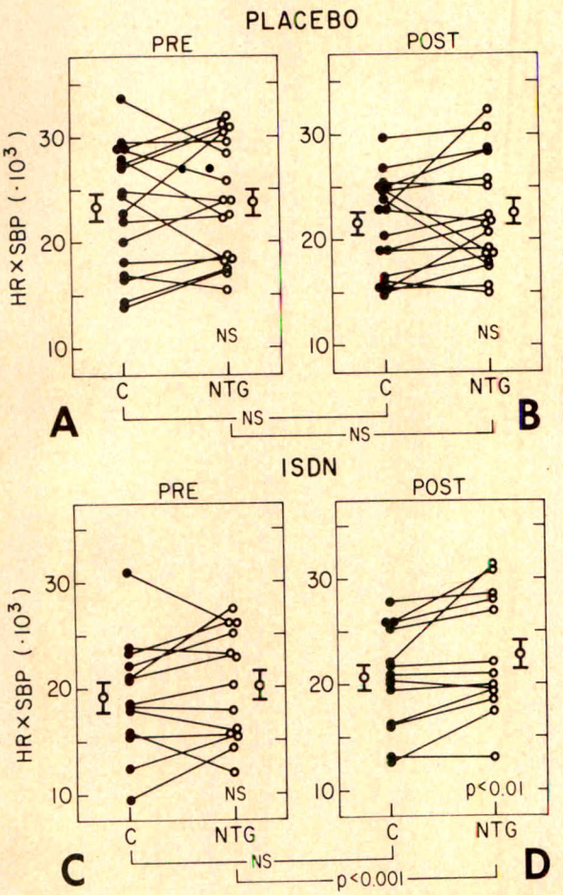

FIGURE 5. Group data for heart rate-systolic blood pressure (HR × SBP) (× 10^3). Presentation of data and abbreviations as in Figure 3.

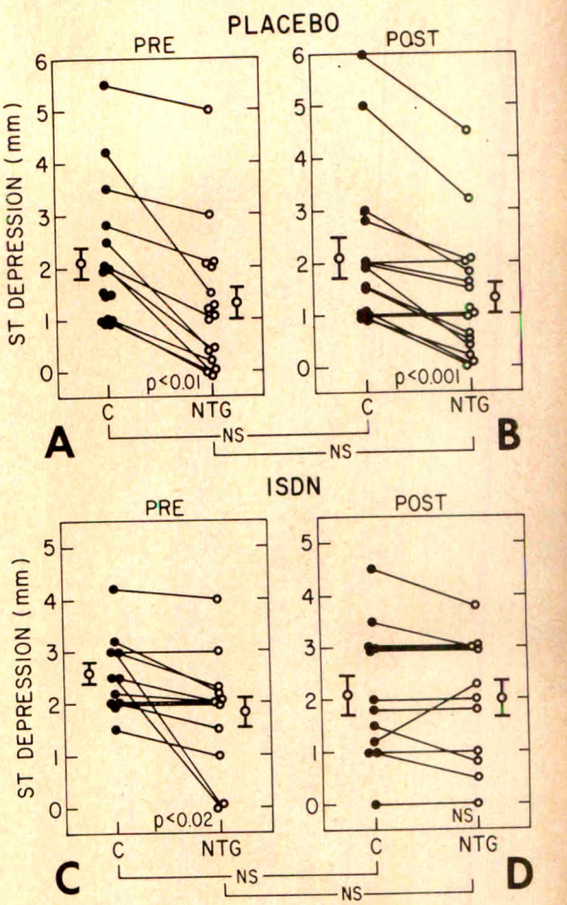

FIGURE 6. Group data for electrocardiographic S-T depression (mm). Presentation of data and abbreviations as in Figure 3.

spectively, 1 month of isosorbide dinitrate therapy. Thus, maximal achievable derived oxygen consumption was identical ($P < 0.05$) after the administration of nitroglycerin in the periods before and after isosorbide dinitrate therapy. Consistent with the increase in exercise duration, derived maximal oxygen consumption during exercise before nitroglycerin was greater ($P < 0.001$) after 1 month of isosorbide dinitrate therapy.

Heart rate-blood pressure product: Data regarding heart rate-blood pressure product are depicted in Figure 5. Maximal heart rate-blood pressure product, expressed to 10^3, was unchanged before and after the administration of nitroglycerin, from 23.3 ± 1.4 to 23.7 ± 1.3 ($P > 0.05$) (Fig. 5A) and from 21.6 ± 1.1 to 22.6 ± 1.2 ($P > 0.05$) (Fig. 5B) before and after, respectively, the administration of placebo capsules. Similarly, heart rate-blood pressure product at maximal exertion was not statistically different in the preisosorbide dinitrate period before and after the sublingual administration of nitroglycerin: from 19.2 ± 1.5 to 20.2 ± 1.5 ($P > 0.05$) (Fig. 5C). After isosorbide therapy, a minimal increase in the maximal level of this variable reaching statistical significance was observed after the sublingual administration of nitroglycerin: 22.8 ± 1.6 compared with the prenitroglycerin value of 20.7 ± 1.4 ($P < 0.01$) (Fig. 5D).

S-T segment depression: Regarding the quantity of S-T segment depression observed at maximal exertion (Fig. 6), nitroglycerin produced a significant reduction in this electrocardiographic abnormality, from 2.1 ± 0.3 to 1.3 ± 0.3 mm ($P < 0.01$) (Fig. 6A) before and after, respectively, ($P < 0.001$) (Fig. 6B) 1 month of placebo. S-T segment depression at maximal exertion in the group given isosorbide dinitrate was similarly reduced after nitroglycerin in the premedication period, from 2.6 ± 0.2 to 1.8 ± 0.3 ($P < 0.02$) (Fig. 6C). However, the extent of S-T segment depression manifested in the prenitroglycerin exercise electrocardiogram after administration of isosorbide was substantially less than that observed in the control period before its administration. Thus, although the S-T segment depression at maximal exertion observed after nitroglycerin was identical before and after oral administration of isosorbide dinitrate, the maximal degree of S-T segment depression after isosorbide was similar before and after nitroglycerin: from 2.1 ± 0.4 mm prenitroglycerin to 2.0 ± 0.3 mm postnitroglycerin ($P > 0.05$) (Fig. 6D). Thus, the ability of sublingually administered nitroglycerin to augment exercise duration and maximal oxygen consumption without a concomitant increase in electrocardiographic evidence of myocardial ischemia was maintained after long-term administration of isosorbide dinitrate.

Percent alteration in exercise variables: Subsequently, we analyzed the percent change from control values induced by sublingual administration of nitroglycerin in the periods before and after the administration of placebo and isosorbide dinitrate. No change in the percent increase in duration of exercise and the derived index of oxygen consumption or the decrease in S-T segment depression induced by nitroglycerin was observed from the pre- to postplacebo periods: from 37 to 25 percent, from 17 to 12 percent and from 40 to 40 percent, respectively (all $P > 0.05$). After administration of isosorbide, a significant augmentation of exercise duration and derived oxygen consumption and a substantial decrease in S-T segment depression were observed even before the administration of nitroglycerin. Consequently, reductions in the percent increase in exercise duration induced by nitroglycerin (from 38 to 13 percent), derived oxygen consumption (from 19 to 7 percent) and decrease in S-T segment depression (from 29 to 3 percent) (all $P < 0.05$) were calculated after therapy with isosorbide even though the further alterations in these variables effected by nitroglycerin resulted in values identical to those achieved in the pre-isosorbide period after nitroglycerin.

Discussion

The recent demonstration of the value of orally administered sustained-release isosorbide dinitrate in the prophylactic therapy of angina pectoris has led to the increased application of this agent in patients with ischemic heart disease.[3,4,6–13] In addition, isosorbide has also been utilized as a ventricular unloading agent in the treatment of chronic congestive heart failure.[14] Thus, the question whether isosorbide dinitrate administered orally in large doses induces the development of tolerance, especially in regard to cross-tolerance to sublingually administered nitroglycerin, has assumed greater importance.

Cross-tolerance to nitroglycerin after long-acting isosorbide dinitrate: Although the propensity for long-acting organic nitrates to induce cross-tolerance to nitroglycerin has been suspected for many years, clinical investigations of this tendency have been few and have yielded conflicting data. Thus, Schelling and Lasagna[15] noted a slight attenuation in the decrease in systemic blood pressure and reflex tachycardia produced by sublingually administered nitroglycerin after 4 weeks of pentaerythol tetranitrate. Additionally, Zelis and Mason,[16] utilizing plethysmography, observed a reduction in venodilation but not arteriolar dilation in response to sublingually administered nitroglycerin after the oral administration of isosorbide dinitrate for 6 weeks. In contrast, Goldstein et al.[17] observed no alteration in the response of physiologic measurements or exercise tolerance to sublingually administered isosorbide dinitrate after long-term administration; and Aronow and Chesluk[19] observed the identical antianginal effect of sublingually administered nitroglycerin before and after prolonged use of isosorbide dinitrate. However, in the two latter studies, the dose of oral nitrate utilized was not as large as that required for effective prophylactic therapy of angina pectoris.

Our investigation indicates that cross-tolerance to the antianginal effect of sublingually administered nitroglycerin is not induced by the long-term oral administration of isosorbide dinitrate in large doses. Thus, maximal duration of exercise, derived index of oxygen consumption, heart rate-blood pressure product and S-T segment depression after nitroglycerin was identical before and after long-term administration of the long-acting nitrate preparation (Fig. 3 to 6). In addition, because exertional capacity, oxygen consumption and S-T segment depression were improved in the control period after 1 month of isosorbide therapy, but not after placebo, no major tolerance to isosorbide dinitrate itself was evident. However, our study was not specifically designed to evaluate tolerance to isosorbide itself, and it is possible that minor degrees of tolerance could have been overlooked.

Effect of long-term isosorbide therapy on clinical antianginal effect of nitroglycerin: Previous studies[15,16] indicating that long-term administration of long-acting organic nitrates induces cross-tolerance to nitroglycerin dealt with isolated measures of cardiocirculatory function such as systemic blood pressure and forearm venous tone. Accordingly, no inferences could be drawn from these reports regarding the influence of long-term nitrate administration upon the clinical antianginal effect of nitroglycerin. In our investigation, exercise stress testing provided an objective method for evaluating the influence of long-term isosorbide dinitrate therapy on the clinical antianginal effects of nitroglycerin. Previous studies[20] have indicated that maximal exercise capacity during treadmill walking is readily reproducible in patients with coronary artery disease after an initial educational experience. That peak exertion is indeed constant was well demonstrated by the identical values recorded for both exercise duration and derived index of maximal oxygen consumption before and after placebo therapy (Fig. 3 and 4). Thus, the finding that nitroglycerin induced the same duration of exercise and derived maximal oxygen consumption with equivalent S-T segment depression after and before long-acting isosorbide dinitrate therapy constitutes strong objective evidence that the latter does not induce cross-tolerance to the clinical antianginal effects of nitroglycerin.

Our data were also analyzed in regard to percent improvement in those measurements manifesting a response to sublingually administered nitroglycerin. No differences were noted in any of the exercise functions assessed after as compared with before placebo. Conversely, reductions in the percent increase in exercise duration and the derived index of oxygen consumption and decrease of S-T segment depression induced by nitroglycerin were observed after administration of isosorbide dinitrate. However, this diminution in the percent change in response to nitroglycerin was referable entirely to alterations in these values produced by the sustained action of isosorbide dinitrate in the control period. Thus, significant increases in exercise duration and derived oxygen consumption and a substantial decrease in S-T segment depression occurred before the administration of nitroglycerin after 1 month

of isosorbide therapy. Nevertheless, nitroglycerin was still able to augment further these beneficial effects to levels identical with those produced before isosorbide administration (Fig. 6). Thus, patients continued to achieve the same maximal duration of exercise and derived oxygen consumption in response to nitroglycerin without additional S-T segment depression after isosorbide dinitrate therapy as before administration of this agent.

Although heart rate-blood pressure product does not account for all the determinants of myocardial oxygen demand, it has been demonstrated to represent a relatively accurate index of this function.[21] Thus, interventions that enable greater duration of exercise and maximal oxygen demand by virtue of increasing myocardial oxygen supply (such as coronary artery bypass surgery) are associated with increases in heart rate-blood pressure product.[22] The observation that the rate-pressure product was unchanged at maximal exertion after nitroglycerin in our study supports the concept that the increase in exercise capacity produced by this agent is referable to a decrease in myocardial oxygen demand. Although the maximal rate-pressure product increased slightly after nitroglycerin during exercise testing after isosorbide dinitrate therapy, the change was considered too small to be of substantial physiologic significance.

In our study, isosorbide dinitrate was administered in large doses for 1 month. That this period is sufficiently long to induce cross-tolerance to nitroglycerin is indicated by the finding in two previous studies[15,16] that circulatory responsiveness to nitroglycerin was reduced in a similar period of time. In addition, headaches precipitated by nitrates have characteristically been observed to disappear within a few weeks.[23,24] Finally, evidence of cross-tolerance to the vasodilator effects of nitroglycerin has been recorded after only 3 days of long-term nitrate administration in rats.[25]

In conclusion, our data indicate that cross-tolerance to the antianginal effect of sublingually administered nitroglycerin is not induced by long-term oral administration of isosorbide dinitrate. Although previous studies have reported evidence suggesting the development of cross-tolerance to nitroglycerin induced by long-acting nitrates, such small changes in circulatory function apparently do not impair the clinical antianginal effect of this agent.

Acknowledgment

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Effects of Ouabain on Coronary and Systemic Vascular Resistance And Myocardial Oxygen Consumption in Patients Without Heart Failure

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The effect of digitalis glycosides on vascular resistance varies from one vascular bed to another and is also related to the hemodynamic state of the patient. To determine whether the rate of infusion is also a determinant of the vasoactive response the effect of various infusion rates of ouabain on the coronary and systemic beds was examined and the associated changes in myocardial oxygen consumption in patients without heart failure were quantitated. A 10 second and 2 minute infusion of ouabain (15 μg/kg body weight) produced 18.1 ± 5.6 percent and 7.5 ± 1.7 percent increases in mean arterial pressure and 23.7 ± 9.8 percent and 17.6 ± 7.5 percent increases in systemic vascular resistance, respectively ($P < 0.05$ for each). A 15 minute infusion produced no statistically significant change in either variable. Coronary vascular resistance increased 13.4 ± 5.2 percent ($P < 0.05$) after a 10 second infusion but did not change during or after a 15 minute infusion. The 10 second infusion was also associated with transient deterioration of myocardial lactate metabolism. Thirty minutes after ouabain administration mean arterial pressure had returned to control levels, but myocardial oxygen consumption remained increased by 12.5 ± 3.9 percent ($P < 0.025$), indicating that ouabain produces a net increase in myocardial oxygen demand in patients without heart failure.

Rapid intravenous administration of ouabain produces systemic and coronary arteriolar constriction that may lead to clinical deterioration. These effects can be avoided by slower delivery of the drug. Even in patients without heart failure, the increase in myocardial oxygen consumption with full digitalization is small.

Digitalis glycosides are usually administered clinically for their inotropic or electrophysiologic effects. However, they also alter vascular tone, and this effect may significantly influence the outcome of therapy. The effect of digitalis on vascular tone depends on several factors. The extent and direction of changes in vascular tone depend on whether or not heart failure is present.[1] In the experimental animal the magnitude and direction of the effect varies from one vascular bed to another.[2] In addition, if ischemia were to be produced by digitalis-induced vasoconstriction, the response might be modified by local metabolic factors. Although many studies have demonstrated the vasoconstrictive ability of digitalis in man, several studies[3,4] have shown little or no effect when the drug is given slowly rather than as a bolus injection. Thus, the rate of infusion of digitalis may also be an important determinant of changes in vascular resistance. Indeed, the vasoconstrictive ability of digitalis in the coronary circulation of man remains to be demonstrated. The lone previous study[5] showed no effect and its results conflict with the data accumulated in experimental animals.

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TABLE I

Effects of Ouabain on the Systemic Circulation at Various Rates of Ouabain Infusion

	Minutes After Onset of Ouabain Administration							
	2	4	6	8	12	15	30	45
Mean arterial pressure								
10 sec	10.0 ± 2.3*	18.8 ± 3.5*	18.1 ± 5.6*	15.4 ± 5.3*	10.5 ± 7.0	9.8 ± 4.7	5.5 ± 3.8	. . .
2 min	3.1 ± 1.3	6.4 ± 1.9*	7.5 ± 1.7*	7.0 ± 2.4	3.6 ± 2.8	3.1 ± 2.2	1.7 ± 1.5	. . .
15 min	. . .	1.3 ± 1.5	. . .	3.0 ± 1.8	8.0 ± 3.7	2.4 ± 5.9	2.6 ± 1.8	4.6 ± 3.6
Cardiac output								
10 sec	−2.7 ± 2.8	−0.6 ± 4.4	−2.4 ± 4.1	14.1 ± 11.3	14.2 ± 14	8.4 ± 6.9	8.6 ± 8.8	. . .
2 min	0.3 ± 1.2	−5.4 ± 4.1	−7.5 ± 4.5	−8.3 ± 3.2*	−6.8 ± 4.5*	−2.0 ± 5.0	4.4 ± 6.1	. . .
15 min	. . .	1.6 ± 3.6	. . .	0.5 ± 3.3	4.5 ± 4.3	9.1 ± 4.7	11.9 ± 4.2	16.0 ± 6.9
Systemic vascular resistance								
10 sec	16.8 ± 3.9*	22.6 ± 6.3*	23.7 ± 9.8	6.1 ± 8.1	2.3 ± 10.6	3.4 ± 5.3	0.7 ± 8.7	. . .
2 min	3.7 ± 1.6	13.7 ± 6.6	17.6 ± 7.5*	15.4 ± 4.7*	12.8 ± 9.1	12.0 ± 6.7	−2.6 ± 6.5	. . .
15 min	. . .	−2.9 ± 2.6	. . .	1.2 ± 2.7	0.9 ± 3.8	−5.5 ± 5.1	−6.0 ± 4.5	−12.0 ± 5.5

All values represent percent change from control (mean ± standard error of the mean).
* $P < 0.05$.

In this study of patients without heart failure we determined the time course of changes in coronary and systemic vascular resistance with various rates of infusion of ouabain, quantitated the increase in myocardial oxygen consumption produced and related these changes to changes observed in myocardial metabolism.

Material and Methods

Patients: A total of 36 patients were studied, 22 to evaluate the effects of ouabain on the systemic circulation and 14 to evaluate its effects on the coronary circulation. The patients had a mean age of 59 years (range 33 to 81 years). No patient manifested clinical evidence of congestive heart failure. The mean right atrial pressure was 4 mm Hg or less in each patient. The pulmonary arterial wedge pressure or left ventricular end-diastolic pressure was less than 12 mm Hg in each of the 17 patients in whom it was measured. No patient manifested cardiomegaly in the chest roentgenogram. Two patients had previously received digitalis glycosides, but neither had received these agents within the 3 weeks preceding the study. The dose of ouabain in this study was 15 μg/kg body weight. Informed consent was obtained from each patient before study.

Systemic circulation: Thirteen of 22 patients whose systemic circulation was evaluated had coronary artery disease as judged from a classical history of angina pectoris or myocardial infarction. In 4 of these 13 the diagnosis was confirmed with angiography. The remaining nine patients were studied during the course of evaluation for conduction system abnormalities.

Brachial arterial and right atrial pressures were monitored using fluid-filled catheter systems. Cardiac output was measured with the indicator-dilution technique using either indocyanine green or cold saline solution. Eight patients were given a 15 minute infusion of ouabain, seven patients a 2 minute infusion and seven patients a 10 second infusion. Cardiac output measurements were made at 2, 4, 6, 8, 12, 15 and 30 minutes in the 10 second and 2 minute infusion groups and at 4, 8, 12, 15, 30 and 45 minutes in the 15 minute infusion group. Systemic vascular resistance was calculated as the quotient of the decrease in pressure from the brachial artery to the right atrium and the cardiac output.

Coronary circulation: Of the 14 patients whose coronary circulation was studied, 7 were being evaluated for coronary artery disease that was confirmed with coronary angiography. Of seven other patients who were being studied for conduction system abnormalities three had classical angina pectoris. Thus 10 of the 14 patients had coronary artery disease. Mean arterial pressure was measured continuously using a brachial arterial catheter. Coronary sinus flow was measured using the thermodilution technique of Ganz et al.[6] at 2, 4, 6, 8, 12, 15 and 30 minutes after initiation of the infusion of ouabain. Coronary vascular resistance was calculated as the quotient of the decrease in pressure from the brachial artery to the coronary sinus and the coronary sinus flow.

Myocardial oxygen supply and demand: Blood samples were obtained from the coronary sinus and from the brachial artery before and 6 to 8, 15 and 30 minutes after initiation of the infusion of ouabain. Oxygen content was calculated from the partial pressure of oxygen, pH and hemoglobin concentration using a Severinghaus nomogram.[7] Myocardial oxygen consumption was calculated as the product of the arterial coronary venous oxygen difference and coronary sinus flow. Lactate concentration was determined with use of a technique described previously.[8]

Statistical analysis: The percent change from control value was determined for each variable at each time period and the significance of changes from the control value determined using a paired t test.

Results

Systemic circulation: Mean arterial pressure increased at each of the three rates of infusion of ouabain (15 minutes, 2 minutes and 10 seconds). The extent of increase in mean arterial pressure decreased progressively as the rate of infusion was prolonged, and statistically significant changes from control values were observed only in the 10 second and 2 minute infusion groups (Table I). The increases in arterial pressure in the 10 second and 2 minute infusion groups were accompanied by decreases in cardiac output, whereas a slight increase in arterial pressure in the 15 minute infusion group was accompanied by a small increase in cardiac output. Only the reduction in cardiac output in the 2 minute infusion group was statistically significant.

Systemic vascular resistance increased abruptly in the 10 second infusion group, reaching a peak within 6

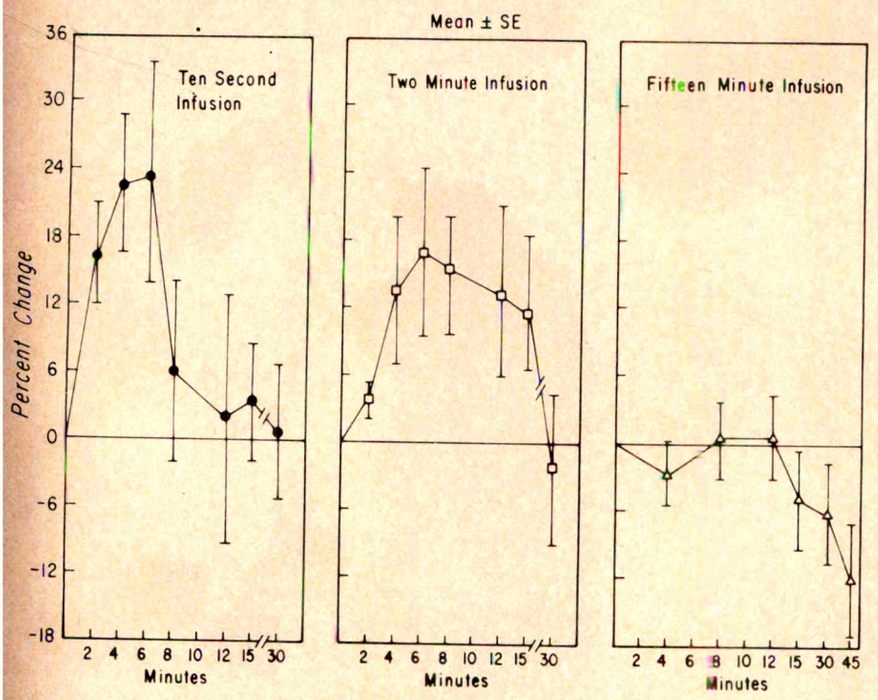

FIGURE 1. Effect of ouabain on systemic vascular resistance shown as percent change from control for three rates of infusion. SE = standard error of the mean.

minutes of infusion (Fig. 1). Maximal increases ranged from 12 to 66 percent (mean 31.7 percent). Lesser changes occurred in the 2 minute infusion group in which increases ranged from 7 to 52 percent (mean 24 percent). The time of peak changes occurred at either 2 or 4 minutes in the 10 second infusion group and either 6 or 8 minutes in the 2 minute infusion group. No significant changes in systemic vascular resistance occurred at any time in the 15 minute infusion group.

Coronary circulation: The changes in mean arterial pressure induced by ouabain in this group of 14 patients (Table II) were similar to those found at at the corresponding infusion rates in the first portion of the study (systemic circulation, see preceding). No change occurred in right atrial pressure. Coronary blood flow decreased in five of seven patients given a 10 second infusion of ouabain. The mean change was a reduction of 8.0 ± 7.4 percent ($P > 0.05$) at 2 minutes. Subsequently coronary blood flow remained near control levels. No significant change occurred at any time in the group of patients given a 15 minute infusion. Coronary vascular resistance increased abruptly in the 10 second infusion group but decreased to near preinfusion levels by the end of the period of observation (Fig. 2). No significant change in coronary vascular resistance occurred at any time in the 15 minute infusion group.

Myocardial oxygen supply and demand: Myocardial oxygen consumption increased in both the 10 second and 15 minute infusion groups. In the 10 second infusion group the increase was 15.6 ± 5.2 percent, 14.0 ± 5.6 percent and 13.7 ± 4.1 percent at 8, 15 and 30 minutes. At the corresponding times the increases in the

TABLE II

Effects of Ouabain on the Coronary Circulation at Various Rates of Infusion

	Minutes After Onset of Ouabain Administration						
	2	4	6	8	12	15	30
Mean arterial pressure							
10 sec	9.3 ± 1.9*	9.6 ± 3.3*	11.4 ± 3.0*	10.4 ± 3.2	7.4 ± 2.6	6.7 + 2.3	1.5 ± 3.2
15 min	. . .	3.5 ± 1.1	. . .	4.3 ± 0.9	3.5 ± 3.0	−2.2 ± 3.3	2.8 ± 2.9
Coronary sinus flow							
10 sec	−8.0 ± 7.4	−1.8 ± 6.4	0.1 ± 5.3	−0.6 ± 4.0	−0.4 ± 4.2	−0.4 ± 4.2	0.6 ± 10.1
15 min	. . .	1.8 ± 4.8	. . .	5.1 ± 3.4	−1.2 ± 2.4	2.7 ± 5.5	3.0 ± 5.7
Coronary vascular resistance							
10 sec	9.8 ± 6.3	13.7 ± 7.6	13.5 ± 5.2*	11.8 ± 5.9	9.4 ± 5.4	4.7 ± 6.2	3.8 ± 10.9
15 min	. . .	2.0 ± 6.6	. . .	0.9 ± 2.4	0.5 ± 2.9	1.0 ± 6.9	4.1 ± 5.0

·All values represent percent change from control (mean ± standard error of the mean).
* $P < 0.05$.

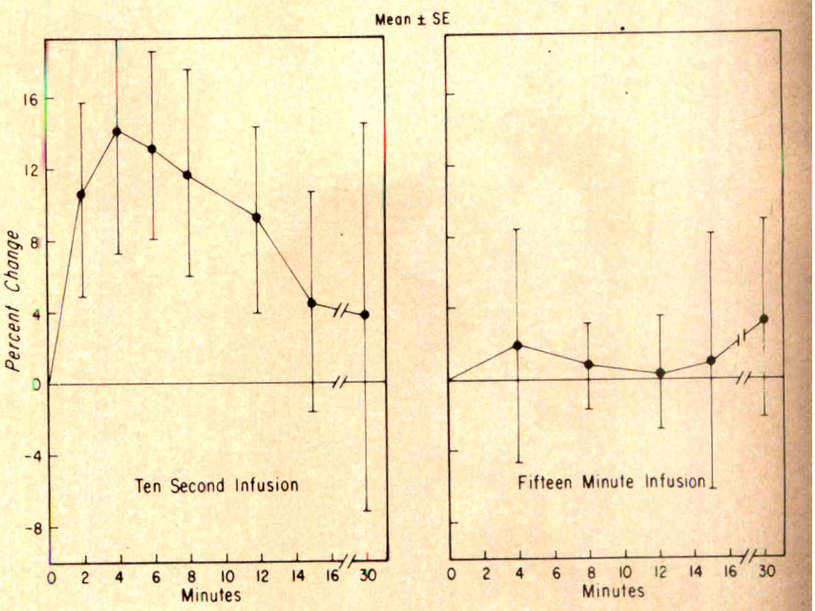

FIGURE 2. Effect of ouabain on coronary vascular resistance shown as percent change from control values after 10 second and 15 minute infusions. SE = standard error of the mean.

15 minute infusion group were 10.3 ± 5.8 percent, 11.1 ± 10.4 percent and 12.1 ± 5.8 percent. The difference between the two groups was not significant. At the end of 30 minutes when vascular resistance had returned to near control levels in both groups myocardial oxygen consumption had increased 12.5 percent from 13.5 ± 0.94 to 15.1 ± 1.09 ml O_2/min (P <0.025), indicating that ouabain increases myocardial oxygen consumption in patients who do not have heart failure (Fig. 3).

Lactate extraction decreased at 6 minutes in all patients given a 10 second infusion. In two patients lactate extraction reverted to lactate production and in one patient with resting lactate production lactate metabolism deteriorated further. The mean decrease in the percent of lactate extraction was 7.7 ± 1.2 percent at 8 minutes (P <0.05). However, as coronary vascular resistance decreased, lactate extraction improved to 0.5 ± 2.6 percent (P >0.05) and 12.7 ± 2.3 percent (P <0.05) at 15 and 30 minutes, respectively. In the group with the slow infusion rate lactate extraction increased in all but one patient who had a transient decrease. The increase in extraction was 12.4 ± 4.8, 15.7 ± 5.1 and 7.3 ± 3.7 percent at 8, 15 and 30 minutes, respectively (P <0.05 at 8 minutes). One of the two patients in this group with resting lactate production manifested lactate extraction, and the other produced less lactate. Thirty minutes after initiation of the infusion the two groups were similar (Fig. 4).

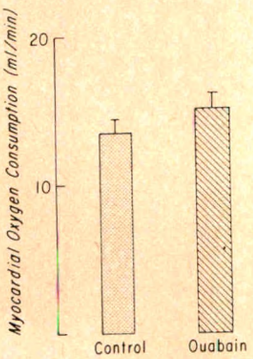

FIGURE 3. Increase in myocardial oxygen consumption induced by ouabain in patients without heart failure (P <0.025 by paired t test). Although the increase is small, it is statistically significant because values in each patient changed in the same direction.

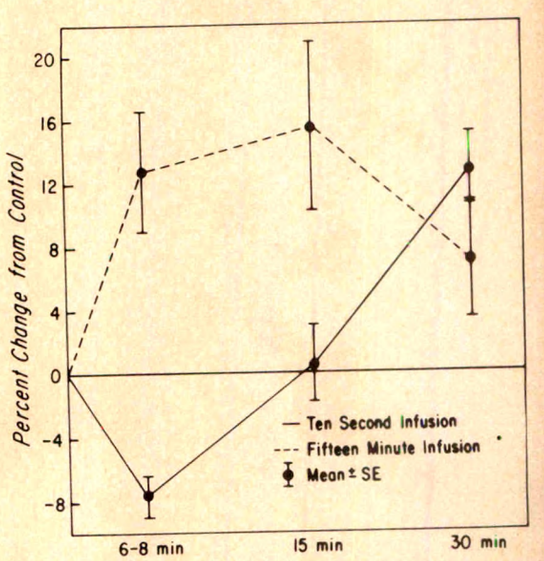

FIGURE 4. The mean absolute percent change from control values in myocardial lactate extraction or production shown for patients receiving 10 second and 15 minute infusions of ouabain. SE = standard error of the mean.

Discussion

Systemic circulation: Digitalis glycosides are able to produce arteriolar constriction in every vascular bed that has been tested.[1,2,9–12] The effect of glycosides was shown to vary in intensity from one vascular bed to another and was even biphasic in the mesenteric vascular bed of conscious animals.[2] In that study simultaneously recorded changes in the iliac vascular bed were approximately twice those found in the mesenteric and renal vascular beds. The effect of glycosides on vascular tone also varies with the underlying hemodynamic state of the patient; that is, with heart failure vasodilation occurs after digitalis administration and without heart failure vasoconstriction occurs.[1] Our study demonstrates that systemic vasoconstriction resulting from digitalis administration is also a function of the rate of infusion of ouabain and does not occur if the rate of infusion is prolonged to 15 minutes. Because this period of time is far short of the 22 hour serum half-life of ouabain, drug excretion does not explain our findings.[13]

Most of the clinical effects of peripheral vasoconstriction are deleterious, although part of the efficacy of digitalis in converting atrial tachyarrhythmias may reside in its ability to increase arterial pressure when given rapidly. However, after rapid infusion of digoxin, a hypertensive crisis resulting in a stroke occurred in one patient[14] and induction of pulmonary edema in another.[15] Numerous cases of nonocclusive splanchnic infarction have occurred, usually in the setting of chronic digitalis administration.[16,17] However, preexisting circulatory failure and widespread atherosclerosis are commonly found in patients with splanchnic infarction, and the contribution of digitalis is difficult to assess.

These observations are also relevant to the patient with cardiogenic shock[15] in whom it has been postulated that the circulatory state may deteriorate because the peak afterload effect of digitalis precedes the peak inotropic effect.[11,18] This association is also difficult to assess because patients with cardiogenic shock are frequently not in a stable clinical state and are prone to clinical deterioration even without intervention. However, it would be unwise to administer digitalis rapidly to a patient with cardiogenic shock when vasoconstriction may be avoided by slower infusion.

Coronary circulation: A previous study[5] examining the effect of strophanthus on coronary vascular resistance showed no effect 22 minutes after administration. However, the nitrous oxide technique employed in that study is not suitable for rapid measurement of coronary blood flow, and the effect of strophanthus was determined only once after its administration. Our data suggest that the effect of the drug had dissipated at the time of the postinfusion measurement in that study. Digitalis is able to produce an increase in coronary vascular resistance, but the effect is not of long duration and can be avoided completely by slow administration of the drug.

Digitalis exerts its effects by acting directly on arteriolar smooth muscle and by a neurogenic mechanism activated by alpha adrenergic receptors,[19] probably located in the central nervous system.[20] Digitalis also alters sympathetic tone indirectly by increasing baroreceptor sensitivity. Therefore the changes in vascular resistance produced by digitalis in patients with increased sympathetic tone such as those with congestive heart failure may be different from the changes observed in our study.

Myocardial oxygen supply and demand: The potential for deleterious effects in the ischemic myocardium resulting from arterial vasoconstriction is of special importance. The effect of digitalis on myocardial oxygen consumption (MVO_2) is complex. We have previously shown that ventricular end-diastolic volume decreases even in patients who do not have congestive heart failure.[8] However, MVO_2 increases in these patients because the cost of the enhanced contractile state exceeds the decrease in MVO_2 associated with a reduction in end-diastolic volume and wall tension. An increase in afterload such as we have demonstrated after rapid administration of ouabain would tend to increase MVO_2 further. However, coronary vasoconstriction does not allow an increase in coronary blood flow despite the increased perfusion pressure. As a result, lactate metabolism deteriorated (Fig. 4). In contrast, when a slow infusion of ouabain was given the hypertensive and coronary vasoconstrictive responses did not occur and changes in lactate extraction were favorable (Fig. 4). Thus, the rate of infusion may be a crucial variable to consider when evaluating the effects of digitalis on augmentation or decrease in infarct size in man or in experimental myocardial infarction.

Our study also demonstrates that whether digitalis is given rapidly or slowly, MVO_2 increases in patients who do not have heart failure, confirming observations that we have made previously.[8]

Myocardial oxygen consumption, calculated as the product of coronary sinus flow and arterial coronary venous difference, may not be identical to myocardial oxygen needs if myocardial ischemia results. The disparity in lactate metabolism between the groups with the rapid and slow infusion rates suggests a difference in the ratio of oxygen supply to oxygen need. Thus, a real difference in oxygen needs of the myocardium may have been present even though the difference in myocardial oxygen consumption between the two groups was not statistically significant.

Implications: The balance between myocardial oxygen supply and demand is critical in patients with coronary artery disease. Changes in myocardial oxygen consumption after administration of digitalis are least favorable in patients without heart failure, but even in these patients the cost appears relatively small. Our study suggests that possible deleterious effects of glycosides in experimental myocardial infarction[21] and in patients with myocardial infarction[22] may be more closely related to the vasoconstrictive properties of digitalis than to changes in myocardial oxygen consumption. Moreover, the vasoconstrictive changes may be avoided by slow administration of the drug.

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Termination of Ventricular Tachycardia With Bursts of Rapid Ventricular Pacing

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Bursts of rapid ventricular pacing used during 573 episodes of ventricular tachycardia in 23 patients terminated 512 episodes (89 percent), with burst rates averaging 56 beats/min above the ventricular tachycardia rate, for 5 to 10 captures. Tachycardia was accelerated by pacing bursts to rates below 300 beats/min in 16 episodes (3 percent); 10 of these terminated spontaneously or responded to further bursts. Acceleration of heart rate to more than 300 beats/min or ventricular fibrillation occurred six times (1 percent), each episode requiring direct current cardioversion. Pacing bursts had no effect in 38 instances (7 percent), mostly in patients with terminal cardiogenic shock. Implantable pacemakers delivering bursts of rapid ventricular pacing were placed in two patients who have used these units at home. No deaths were associated with bursts of rapid ventricular pacing, which is an effective, rapid, pleasant alternative to repeated direct current cardioversion and a useful tool during electrophysiologic testing in patients with recurrent ventricular tachycardia.

Ventricular tachycardia has been terminated by pacing at rates just in excess of the ventricular rate and then slowly decreasing the rate.[1] Random[2] or programmed extrasystoles[3–7] may terminate ventricular tachycardia. These techniques for pacemaker cardioversion of ventricular tachycardia are difficult to apply rapidly and require skilled adjustments by the operator of the pacemaker. An exception is the use of a magnet to convert an inhibited pacemaker to asynchronous (competitive) pacing during ventricular tachycardia. Although the magnet can be applied quickly, considerable time may elapse before a stimulus occurs that is precisely timed to terminate the ventricular tachycardia; further, the technique is not useful when two or more stimuli are required for termination of ventricular tachycardia.

Termination of ventricular tachycardia by bursts of rapid ventricular pacing at rates of 190 to 300 beats/min often for several seconds' duration has been reported in small series of one to four cases,[8–11] and we have presented preliminary data on a larger number of cases.[12] Most investigators have remarked on the apparent benignity and effectiveness of this method of cardioversion. We used such pacing in 573 episodes of ventricular tachycardia in 23 patients, gaining an appreciation of the benefits, limitations and complications of bursts of rapid ventricular pacing. Our purpose is to document the effectiveness of this technique in the management of ventricular tachycardia and to compare this method with other pacing techniques. General principles of management of ventricular tachycardia will not be reviewed.

Materials and Methods

Patients

Twenty-three patients received bursts of rapid ventricular pacing during ventricular tachycardia. Group I included 15 patients whose ventricular

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TABLE I

Pharmacologic Trials

	Group I (15 patients)		Group II (8 patients)	
	Patients Treated (no.)	Chronic* Dose	Patients Treated (no.)	Acute Dose (intravenous)
Single drugs				
Propranolol (P)	10	500 mg/day	1	7 mg (1 to 2 mg every 2 min)
Diphenylhydantoin (DPH)	9	500 mg/day	1	750 mg in 45 min
Procainamide (PA)	13	6 g/day	7	10 mg/kg in 15 min *or* 1 g in 50 min
Quinidine (Q)	7	3.2 g/day	1	5 mg/kg
Bretylium (B)	4	2.4 g/day	4	400 mg
Lidocaine	13	100 mg, then 4 mg/min	8	100 mg
Multiple drugs†				
P & DPH	9		0	
P & DPH & PA	6		0	
P & Q	6		0	
P & PA	7		1	
P & B	2		0	
P & PA & B	2		2	
P & PA & B & DPH	2		1	
P & Q & DPH	1		3	
PA & DPH	4		0	
Q & DPH	3		0	
Miscellaneous combinations	5		1	

* Drugs were given in therapeutic trials until these doses were reached in single or combination therapy, unless characteristic side reactions occurred at smaller doses. Individual subjects received larger doses (for example, procainamide 12 g/day). Ultimately successful regimens have been reported elsewhere.[14]

† Plus lidocaine in Group II patients.

tachycardia recurred in spite of drug therapy (Table I) and who underwent serial electrophysiologic-pharmacologic studies, performed as previously described,[13,14] to achieve detailed characterization and control of their arrhythmias. The description and results of electrophysiologic testing to be outlined are limited to pacemaker induction and termination of ventricular tachycardia. Responses to bursts of ventricular pacing were established in the catheterization laboratory, and bursts were often used repeatedly when the patient returned to the cardiac care unit. Informed consent was obtained from all patients.

Group II included eight patients who received bursts of rapid ventricular pacing on an emergency basis at the bedside to terminate recurrent ventricular tachycardia. These were acutely ill patients for whom frequent direct current cardioversion was the alternative and in whom strenuous electrophysiologic testing did not seem appropriate (Table II). Efforts to prevent ventricular tachycardia with drug therapy continued (Table I) but had been unsuccessful before the use of pacing bursts. The patient's clinical status and urgent need for treatment precluded informed consent in three cases, and treatment proceeded in accordance with the hospital's guidelines for such emergencies.

The electrocardiographic diagnosis of ventricular tachycardia was confirmed by evidence in intracardiac electrograms for atrioventricular (A-V) dissociation with fusion beats, retrograde block or similar findings and in Group I patients by the absence of a His bundle potential before the ventricular complex or the presence of a retrograde His bundle potential after the ventricular complex. Atrial and ventricular stimulation studies in Group I patients showed no evidence of anomalous A-V pathways.

Electrophysiologic Studies

Group I, 15 patients: In 10 subjects three multipolar leads were inserted for pacing and recording from the high right atrium, right ventricular apex and the His bundle, low right atrium and right ventricle. Recordings were made using an Electronics for Medicine DR 12 recorder at a paper speed of 100 or 200 mm/sec or a Mingograf 803 recorder. During normal sinus rhythm or ventricular pacing at rates of less than 100 beats/min, programmed extrastimuli were introduced with a Devices type 4279 modular pacing system into the atrium and ventricle to initiate tachycardia. If ventricular tachycardia was not induced, ventricular programmed extrastimuli were given in the ventricular outflow tract and, if necessary, the inflow tract. Techniques including programmed extrasystoles with more rapid pacing rates, exercise or isoproterenol, or both, or repetitive bursts of rapid ventricular pacing at 180 to 300 beats/min for 3 to 6 seconds were used if other methods failed to produce ventricular tachycardia.

TABLE II

Clinical Profile of Patients Receiving Bursts of Rapid Ventricular Pacing

	Group I (15 patients)	Group II (8 patients)
Coronary artery disease	9	8
Without acute infarct	9	1*
Acute myocardial infarction	0	6*
Post cardiac surgery	0	1
Cardiomyopathy	1	0
Other disease	2†	0
Unknown disease	3	0
Male/female ratio	12/3	4/4
Age range (mean)	13–86 (51)	46–75 (66)

* With digitalis toxicity.

† One patient had a prolonged Q-T syndrome; one had Chagas disease.

Five patients arrived in the catheterization laboratory with ventricular tachycardia. Although in hemodynamically stable condition, they were investigated using a single tripolar or bipolar catheter to minimize the time before termination of the tachycardia. No additional leads were inserted in these patients because the electrocardiographic and His bundle recordings confirmed ventricular tachycardia in each and because it was possible with the single catheter to reinduce ventricular tachycardia after its cessation.

Programmed extrastimuli were used in 12 patients during ventricular tachycardia in an attempt to define a window or zone within the cycle when programmed extrastimuli would terminate the arrhythmia. In 10 patients, attempts were made to overdrive the ventricular tachycardia by pacing at rates of 30 or less beats/min in excess of the ventricular rate and then gradually reducing the rate or stopping abruptly.

Treatment with bursts of rapid ventricular pacing for 1 to 3 seconds was used for ventricular tachycardia that did not end spontaneously or after the preceding maneuvers or that was not tolerated by the patient. In the first three subjects, the pacing burst rate was 300 beats/min. Subsequently, initial bursts were at rates of 40 to 50 beats/min faster than the rate of ventricular tachycardia for five to seven captures. If ventricular tachycardia persisted, stimuli resulting in 10 to 12 captures were given at the same pacing burst rate; then if necessary the rate was increased by 25 beats/min reverting to five to seven captures. These steps were repeated until termination or acceleration of ventricular tachycardia occurred. Patients with sustained acceleration of ventricular tachycardia to rates of less than 300 beats/min were treated with further bursts of rapid ventricular pacing. Direct current cardioversion was used if required. Two patients with ventricular rates of more than 300 beats/min were treated with bursts of rapid ventricular pacing. Thereafter, because of rapid hemodynamic decompensation direct current cardioversion was used for all such patients.

Bursts of rapid ventricular pacing were asynchronous*, that is, not based on sensing of the ventricular tachycardia, in all but three patients in whom an orthorhythmic pacer† was used for noncompetitive bursts.

Permanent pacers for termination of ventricular tachycardia by bursts of rapid ventricular pacing were implanted in two Group I patients after serial electrophysiologic-pharmacologic testing.

Group II patients: Eight acutely ill patients with ventricular tachycardia for whom the only alternative treatment was frequent direct current cardioversion were treated with bursts of rapid ventricular pacing at the bedside without formal electrophysiologic studies. Six had acute myocardial infarction with recurrent ventricular tachycardia not prevented by conventional pharmacologic and pacing therapy, one was in the immediate postoperative state after cardiac surgery and one had digitalis toxicity. In six cases the special pacemaker was first set at a low rate in the demand mode (General Electric or orthorhythmic units) to obviate stimulation during the vulnerable period. The rate was then increased until capture was obtained at a rate of 30 or less beats/min in excess of the ventricular tachycardia. After capture was achieved, the rate was decreased or the pacing was stopped abruptly. If ventricular tachycardia persisted, bursts of rapid ventricular pacing were used as described for Group I. In two critical cases, pacing bursts were the initial method used to terminate tachycardia. Programmed extrastimuli were not used in Group II patients because of the much longer time required to establish the termination window.

Patients in Groups I and II were placed in the coronary care unit with a pacemaker capable of delivering bursts of rapid ventricular pacing. House staff members and the nurses were taught to deliver pacing bursts in the event of ventricular tachycardia, while preparations for electrical and pharmacologic cardioversion proceeded concurrently.

Optimal rate for bursts of rapid ventricular pacing: The relation between the rate of tachycardia and the minimal pacing rate for its termination or acceleration was analyzed. The data were not weighted by numbers of episodes; that is, multiple similar episodes of tachycardia in one patient treated with the same pacing burst rate were counted as a single episode, equal to a single episode in another patient. Ventricular tachycardia–bursts of rapid ventricular pacing pairs were used in these calculations only when 1:1 capture occurred.

To derive a clinically useful formula for optimal burst rate, the data described were analyzed by computer (PDP8e, Digital Equipment Corporation, Maynard, Massachusetts) using a curve-fit program and fitted to six curves, representing linear, exponential, power and three hyperbolic functions.

Results

Clinical responses: Bursts of rapid ventricular pacing terminated 512 of 573 episodes (89 percent) of ventricular tachycardia (Tables III and IV). No deaths were related to the use of bursts and no morbidity was associated with insertion of the catheter electrodes. Ventricular tachycardia induced during electrophysiologic studies was identical in rate and configuration to the patient's spontaneous tachycardia.

Five types of responses to bursts of rapid ventricular pacing occurred (Table III): (1) Termination of ventricular tachycardia immediately or after one or more ventricular premature beats after cessation of the burst (see Fig. 1 and 4). (2) Acceleration of ventricular tachycardia to a rate of less than 300 beats/min, often then stopping spontaneously or with further bursts (Table III) (Fig. 2 and 3). (3) Acceleration of ventricular tachycardia to a rate greater than 300 beats/min, or ventricular fibrillation requiring direct current cardioversion. (4) Deceleration of ventricular tachycardia. (5) No effect on the ventricular tachycardia, with or without capture of the ventricle. Bursts of rapid ventricular pacing were more effective than other pacing techniques for termination of ventricular tachycardia (Fig. 1, Table V).

Responses differed greatly among patients but were generally consistent and predictable for each person. No relation existed between administration of digitalis or antiarrhythmic medications and response to bursts of rapid ventricular pacing. Except in the presence of shock, seen only in patients with coronary artery disease, the response to bursts of rapid ventricular pacing did not appear to vary with the underlying disease, although there were too few patients without coronary artery disease to permit a definitive statement. Bursts

* The pacemakers used were: Devices model 4279 (Devices Implants Ltd., Welwyn Garden City, United Kingdom); General Electric model A2071AC; General Electric Co., Milwaukee, Wisconsin; Medtronic model 5320, Medtronic, Inc., Minneapolis, Minnesota; and a pacemaker built by Bioengineering Laboratory, Montefiore Hospital and Medical Center, Bronx, New York.

† Savita Type CSO-RL, distributed by Edwards Pacemaker Systems, Irvine, California. This unit has a sensing circuit that allows programmed extrasystoles or bursts to be given either at a selected interval (in milliseconds) after the last sensed beat, or at an interval that is a selected percentage of the cycle length ("orthorhythmic" mode).

TABLE III

Summary of Responses to Bursts of Rapid Ventricular Pacing

Ventricular Tachycardia	Group I (540 episodes VT)	Group II (33 episodes VT)	Total (573 episodes VT)
Terminated	498(92%)	14(42%)*	512(89%)
Accelerated to a rate of less than 300 beats/min†	14(3%)	2(6%)	16(3%)
Accelerated to a rate greater than 300 beats/min or ventricular fibrillation	6(1%)	0	6(1%)
Decelerated	1(<1%)	0	1(<1%)
Unchanged	24(4%)	17(52%)	38(7%)

* In patients without shock with ventricular tachycardia at a rate of less than 250 beats/min, 11 of 16 episodes (69 percent) were terminated.
† When accelerated, ventricular tachycardia was terminated by further bursts of rapid ventricular pacing (6 episodes), spontaneously (4 episodes) or by direct current cardioversion (6 episodes plus all with a rate greater than 300 beats/min or ventricular fibrillation).

TABLE IV

Responses to Bursts of Rapid Ventricular Pacing: Further Data

	Group I (15 patients)	Group II (8 patients)	Total (23 patients)
Patients (no.) with 1 or more episodes of VT terminated by BRVP	13(87%)	7(88%)	20(87%)
Patients (no.) with 1 or more episodes of VT accelerated by BRVP	8(53%)	2(25%)	10(43%)
Patients (no.) in above group in whom altering BRVP rate and duration prevented acceleration of VT	4(50%)	2(100%)	6(60%)
Patients (no.) in whom BRVP never had effect	1(7%)	1(13%)	2(7%)
Times (no.) BRVP used	712	71	783
Ratio between times BRVP used and termination of VT	1.43	5.07	1.53
Patients (no.) in whom BRVP used for			
1–5 episodes	2	5	7
6–10 episodes	6	3	9
10–20 episodes	4	0	4
90–200 episodes	3	0	3
Patients (no.) receiving digitalis	9(60%)	3(38%)	12(52%)
Patients (no.) in latter group in whom			
VT was terminated once or more	8(89%)	3(100%)	11(92%)
VT was accelerated once or more	6(67%)	1(33%)	7(58%)
Patients (no.) not receiving digitalis*	9(60%)	5(63%)	14(61%)
Patients (no.) in latter group in whom			
VT was terminated once or more	8(89%)	4(80%)	12(86%)
VT was accelerated once or more	4(44%)	1(20%)	5(36%)
Patients (no.) in whom BRVP was used during acute infarction	0	6(75%)	6(26%)
Patients (no.) in latter group in whom			
VT was terminated once or more	...	4(67%)	4(67%)
VT was accelerated once or more	...	2(33%)	2(33%)
Patients (no.) without acute infarction	15(100%)	2(25%)	17(74%)
Patients in latter group in whom			
VT was terminated once or more	13(87%)	2(100%)	15(88%)
VT was accelerated once or more	8(53%)	0(0%)	8(47%)

* The total of 9 patients receiving digitalis and 9 not receiving digitalis in Group I exceeds the total of 15 patients in this group because data are separated for 3 patients who received digitalis during part of the time they received bursts of rapid ventricular pacing. In terms of episodes of ventricular tachycardia, 225 occurred in patients receiving digitalis; 202 (90 percent) were terminated and 8 (4 percent) were accelerated by bursts of rapid ventricular pacing. For patients not receiving digitalis, 310 of 348 episodes (89 percent) were terminated and 14 (4 percent) were accelerated.
BRVP = bursts of rapid ventricular pacing; VT = ventricular tachycardia.

TABLE V

Termination of Ventricular Tachycardia: Comparative Effectiveness of Bursts of Rapid Ventricular Pacing and Other Techniques

	Group I	Group II	Total
Patients in whom ventricular tachycardia (VT) was terminated by			
Bursts of rapid ventricular pacing (BRVP)*	13 of 15 (87%)	7 of 8 (88%)	20 of 23 (87%)
Programmed extrastimuli (PES)†	6 of 12 (50%)	NA	6 of 12 (50%)
BRVP but PES failed	5 of 6 (83%)	NA	5 of 6 (83%)
Overdrive pacing at 30 or less beats/min above rate of VT‡	2 of 10 (20%)	0 of 6	2 of 16 (13%)
BRVP but overdrive failed	8 of 8 (100%)	5 of 6 (83%)	13 of 14 (93%)
PES or overdrive (in patients with both)	5 of 10 (50%)	NA	5 of 10 (50%)
BRVP; both PES and overdrive failed	4 of 5 (80%)	NA	4 of 5 (80%)
PES or overdrive but BRVP failed	0	0	0

* All 23 patients received bursts of rapid ventricular pacing. Of these, 12 received programmed extrasystoles, 16 received overdrive pacing at 30 or less beats/min above the rate of ventricular tachycardia, 10 received both and 5 received neither.
† Six patients received only one programmed extrastimulus in any diastolic interval, three received one and two extrastimuli and three received one, two and three extrastimuli.
‡ Duration of overdrive ranged from a few seconds to 7 minutes.
NA = not attempted.

TABLE VI

Rates (beats/min) of Ventricular Tachycardia (VT) and Bursts of Rapid Ventricular Pacing (BRVP) Resulting in Termination or Acceleration of Ventricular Tachycardia

	VT Rate			BRVP Rate		
	With BRVP Induced Termination of VT	With BRVP Induced Acceleration of VT	P^* <	Resulting in Termination of VT	Resulting in Acceleration of VT	P <
VT rate <200	161 ± 19(15)†	160 ± 11(10)	NS	226 ± 30	267 ± 54	0.025
VT rate ⩾200	234 ± 37(9)	QNS	...	273 ± 42	QNS	...
Overall	188 ± 45(24)	178 ± 32(14)	NS	244 ± 41	270 ± 48	NS 0.10

*P = significance by Student's t test.
†Mean ± standard deviation (number of rate-pacing pairs. See text for derivations of numbers).
NS = not significant; QNS = quantity not sufficient (four instances, as defined in text).

of rapid ventricular pacing terminated ventricular tachycardia in 93 percent of episodes (505 of 544) when the rate of tachycardia was less than 250 beats/min and when the patient's condition was stable. Bursts of rapid ventricular pacing terminated ventricular tachycardia in only 17 percent (5 of 29) when the patient had shock before the onset of ventricular tachycardia, when shock developed or when the rate of the ventricular tachycardia exceeded 250 beats/min.

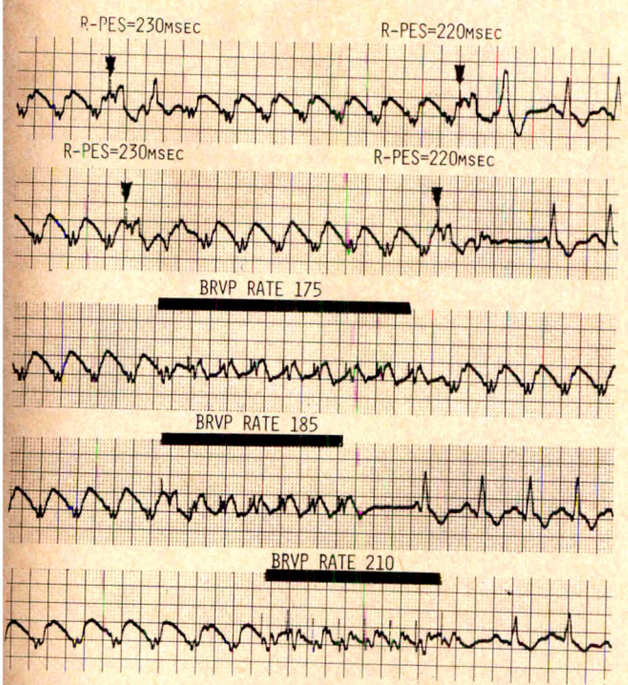

FIGURE 1. Effects of programmed extrastimuli (PES) and bursts of rapid ventricular pacing (BRVP) during ventricular tachycardia. The **top two panels** show ventricular tachycardia at a rate of 150 beats/min reproducibly terminated by programmed extrastimuli 220 (but not 230) msec after the preceding QRS complex **(arrows).** Because the refractory period was 215 msec, the zone during which single extrasystoles were effective was small. In the **third panel,** bursts of rapid ventricular pacing at 175 beats/min **(dark lines)** capture the ventricle, but ventricular tachycardia persists. In the **fourth and fifth panels,** bursts of rapid ventricular pacing at rates of 185 to 210 beats/min for seven to eight captures uniformly terminated the ventricular tachycardia (higher rates were not used in this case). R = R wave.

Cardiac care unit personnel became adept at manual operation of rapid pacemakers. They terminated ventricular tachycardia in 95 percent of more than 100 episodes in patients refractory to medical treatment, usually well before direct current countershock could have been applied. More than 200 episodes of ventricular tachycardia were treated automatically in the cardiac care unit with the orthorhythmic pacer.

Acceleration of ventricular tachycardia by bursts of rapid ventricular pacing: This occurred in 22 of 573 episodes (4 percent) and at least once in 10 of 23 patients (43 percent), including 8 of 15 (53 percent) in Group I and 2 of 8 (25 percent) in Group II. The incidence of acceleration was similar with noncompetitive and asynchronous pacing.

In 6 of 10 patients, recurrent acceleration of ventricular tachycardia by bursts of rapid ventricular pacing could be prevented by altering the rate or duration of the burst. For example, a 33 year old man with cardiomyopathy had ventricular tachycardia at a rate of 180 beats/min that was accelerated by pacing at 280 beats/min or by pacing at 230 beats/min for more than 2.5 seconds; however, bursts at 230 beats/min for 1.5 to 2.0 seconds consistently terminated the tachycardia. In this patient pacing at 10 to 30 beats/min above the rate of ventricular tachycardia captured the ventricle, but the original tachycardia reemerged as the rate was gradually reduced.

In four patients in Group I, each taking different antiarrhythmic medications, acceleration of ventricular tachycardia followed bursts of rapid ventricular pacing, but after a change in medications, there was no acceleration of ventricular tachycardia in response to bursts.

Optimal rate for bursts of rapid ventricular pacing: Analysis in 24 cases using unweighted data revealed that a pacing burst rate of 244 ± 41 (standard deviation) terminated tachycardia at 185 ± 45 beats/min. Overall rates of tachycardia and pacing bursts resulting in acceleration were similar to rates that resulted in termination of tachycardia, but when

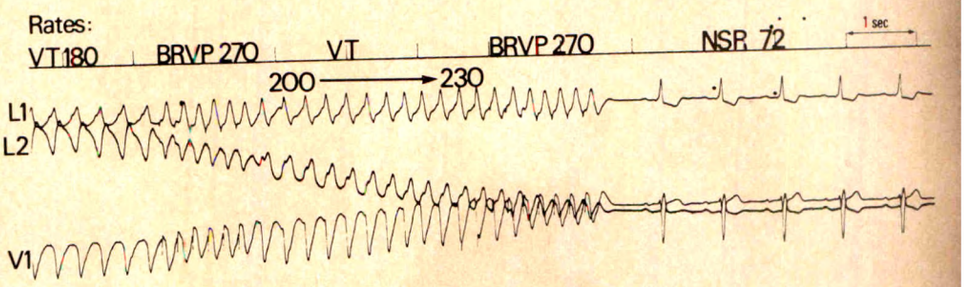

FIGURE 2. Acceleration of ventricular tachycardia (VI) from a rate of 180 to 230 beats/min by bursts of rapid ventricular pacing (BRVP) at 270 beats/min for six captures. The accelerated tachycardia was terminated by further bursts of rapid ventricular pacing. 1 second time lines at top. L1, L2 and V1 = electrocardiographic leads I, II and V_1, respectively; NSR = normal sinus rhythm.

tachycardia rates of less than 200 beats/min were considered separately, faster bursts were significantly more likely to cause acceleration (Table VI).

This analysis provided data on relations between the mean rates of tachycardia and pacing bursts. A formula for optimal burst pacing rate for any given rate of tachycardia was obtained using the curve-fitting program. Best fit was obtained with the linear equation Y = BX + A, with an index of determination of 0.80, where Y is the ventricular tachycardia (VT) rate; B and A are derived constants and X is the burst of rapid ventricular pacing (BRVP) rate. Solving for X will give the pacing burst rate likely to be effective for a given tachycardia rate.* Thus,

$$Y = BX + A$$

$$\text{or VT rate} = B\,(\text{BRVP rate}) + A$$

$$\text{BRVP rate} = \frac{\text{VT rate} - A}{B}$$

For all VT rates,

$$\text{BRVP rate} = \frac{\text{VT rate} + 47}{0.969} \qquad (r = 0.892)$$

For VT rate <200 beats/min,

$$\text{BRVP rate} = \frac{\text{VT rate} - 39}{0.539} \qquad (r = 0.892)$$

For VT rate ≥200 beats/min,

$$\text{BRVP rate} = \frac{\text{VT rate} - 7.3}{0.831} \qquad (r = 0.938)$$

Pacing rates too rapid for 1:1 capture were not included in the preceding calculations but were used for termination of ventricular tachycardia in two patients. One episode ended

* These formulas are useful as general guidelines, but occasionally very different pacing rates may be required. One patient treated after these data were compiled consistently required pacing at 240 beats/min for 12 to 15 captures to terminate a tachycardia at a rate of 140 beats/min. Pacing just in excess of the rate of tachycardia for up to 40 minutes and one to three programmed extrastimuli were ineffective.

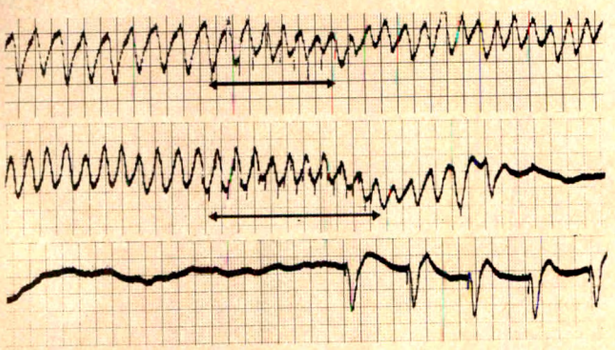

FIGURE 3. Ventricular tachycardia at a rate of 207 beats/min accelerated to 255 beats/min by bursts of rapid ventricular pacing at 350 beats/min **(arrows)** in a patient with terminal cardiogenic shock. In the **middle panel,** after bursts of rapid ventricular pacing at lower rates proved ineffectual, bursts at 780 beats/min resulted in 3:1 ventricular capture and the ventricular tachycardia was replaced by asystole, whereupon pacing at 78 beats/min was instituted. It is possible that this ventricular tachycardia ended spontaneously or that further efforts at lower burst rates would have succeeded, but ventricular capture was not obtained until there was a burst rate of 780 beats/min.

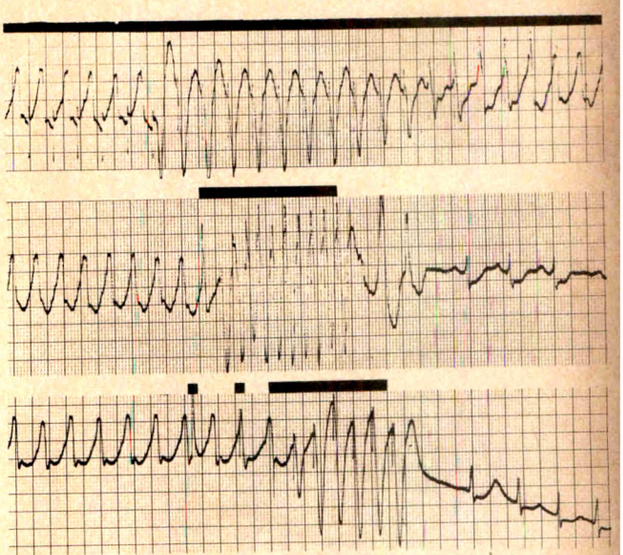

FIGURE 4. Ventricular tachycardia in a patient who later received an implanted pacemaker for bursts of rapid ventricular pacing (see text). **Top panel,** lead II. A ventricular pacemaker is on at 202 beats/min during ventricular tachycardia at 207 beats/min. Capture is obtained but the ventricular tachycardia soon emerges. **Middle panel,** bursts of rapid ventricular pacing at 400 beats/min terminated the episode, but two spontaneous extrasystoles followed. **Bottom panel,** bursts of rapid ventricular pacing at 260 beats/min **(long black bar)** terminated ventricular tachycardia without subsequent extrasystoles. The two pacemaker impulses at a slower rate **(two black squares)** occurred as the General Electric pacemaker was switched from once to twice the indicated rate.

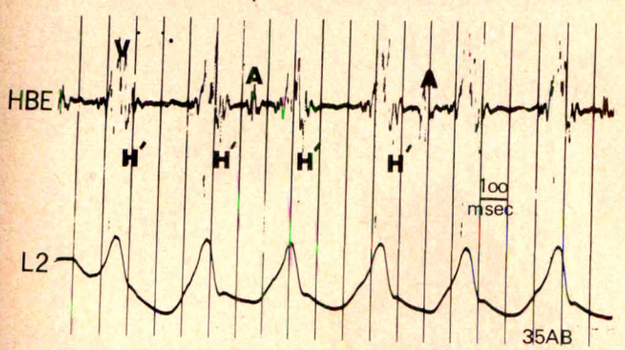

FIGURE 5. Same patient as in Figure 4. Tracing of His bundle electrogram (HBE) during ventricular tachycardia revealing 2:1 ventriculoatrial conduction with retrograde His bundle potentials (H') confirming the diagnosis of ventricular tachycardia.

after pacing at 780 beats/min with 3:1 capture (Fig. 3), lower rates having failed. Rates up to 1,200 beats/min were used in two patients without acceleration of the tachycardia.

Duration of bursts of rapid ventricular pacing: Acceleration of tachycardia could be prevented in some cases by reducing the number of captures. Because asynchronous bursts often begin with stimuli falling ineffectively in the refractory period, the number of captures was analyzed. Determination of the minimal number of captures required to terminate tachycardia was difficult because the number of stimuli or captures could not be precisely controlled with all pacemakers used. Pacing bursts for 4 to 6 captures were often effective and for 7 to 10 captures were usually effective; more than 10 captures were rarely required.

Implantable pacemakers for bursts of rapid ventricular pacing: Permanent pacemakers for termination of ventricular tachycardia by bursts of rapid ventricular pacing were implanted in two patients in Group I after serial electrophysiologic-pharmacologic testing[13–15] failed to establish a fully protective pharmacologic regimen. A 61 year old woman[10] had had for 6 years episodes of ventricular tachycardia at a rate of 200 beats/min that occurred in clusters at approximately 2 week intervals, frequently causing syncope within 10 to 15 seconds. The cause of these episodes was not explained by chemical tests, echocardiography or cardiac catheterization, which yielded normal findings including normalcy of the coronary arteries. The electrocardiogram was normal except for a modest Q-T interval prolongation (QTc interval 0.43 to 0.48). Bursts of rapid ventricular pacing ended 150 episodes (Fig. 4 and 5). An implantable unipolar pacemaker (Cordis Corporation, Miami, Florida) with a ventricular inhibited rate of 81 beats/min was specially constructed. When a magnet was placed over the unit, it emitted a burst of impulses at a rate of 295 beats/min, 8.6 milliamperes with a pulse duration of 1.42 msec, for 2.5 seconds (12 stimuli) and then reverted to pacing at a rate of 81 beats/min. If the ventricular tachycardia was not terminated, the magnet had to be removed and reapplied for another burst. In the 28 months since implantation the patient herself has terminated six episodes that were subjectively identical to her ventricular tachycardia, in each case after a single application of the magnet she keeps.

The second patient, a 33 year old man with congestive cardiomyopathy and ventricular tachycardia at a rate of 180 beats/min, underwent implantation of a Cordis ventricular inhibited pacemaker with an escape rate of 70 beats/min and a magnetically induced rate of 227 beats/min for eight stimuli. He used the unit many times at home and in the hospital, but it was removed after 1 month because ventricular tachycardia occurred more frequently after pacemaker implantation, even after the endocardial lead was repositioned.

Discussion

Advantages of method: For many patients, bursts of rapid ventricular pacing have the advantages of easy application, predictable effectiveness and apparent benignity. Other techniques have important drawbacks. Although one, two or three programmed extrasystoles can terminate tachycardias, they may be less effective, less predictable (Table V) and more time-consuming and require extensive instrumentation and thus may not be suitable for emergency use in a patient in unstable condition. Single random extrasystoles from an asynchronous pacemaker can also terminate ventricular tachycardia, but they take considerably longer than bursts of rapid ventricular pacing to be effective and share with bursts the possibility of stimulation in the vulnerable period. Ventricular tachycardia may sometimes be terminated by gradually increasing the rate of a ventricular inhibited pacer until it exceeds that of the tachycardia, achieving capture and then reducing the rate or turning the pacer off. This does not always work (13 percent success rate in our series) even when a burst of rapid pacing does (Table V).

The peril of myocardial damage induced by repeated direct current countershock may not be great if given through large paddles at intervals exceeding 3 minutes,[16] but such restraint is not always possible when treating recurrent ventricular tachycardia, and there remains the physical and psychologic discomfort to the patient. A burst of rapid ventricular pacing provides quick and painless cardioversion with minimal electrical current.

Mechanism of action of burst pacing: The basis of the effect of bursts of rapid ventricular pacing is not known. It is likely that in reentry arrhythmias the reentry pathway is interrupted just as multiple extrasystoles have been postulated to "peel back" the refractory periods and block reentry.[17,18] This presumption is strengthened because in many patients both programmed extrasystoles and bursts of rapid pacing were successful in terminating the same tachycardia. Bursts of pacing may also terminate ectopic automatic rhythms provided the ectopic focus does not reappear after overdrive suppression.[19,20]

Potential problems and dangers: A problem associated with bursts of rapid ventricular pacing is the possibility of acceleration of the tachycardia. In some patients there was a critical rate and duration "envelope" for success; bursts too slow or too short were ineffective, whereas those that were too rapid or too prolonged caused acceleration. Similar overdrive excitation of ventricular pacemakers by prolonged rapid pacing

has been studied in dogs.[21] Acceleration of ventricular tachycardia without a change in the QRS configuration may result from enhanced automaticity, as observed in the slow response tissue of simian mitral valves[22] or digitalis-poisoned Purkinje fibers,[23] or from an alteration in a microreentry circuit confined to a small volume of myocardium. Acceleration with altered QRS configuration could derive either from altered efferent conduction from an accelerated focus or from a change in the circus pathway.

The risk of ventricular fibrillation caused by bursts of rapid ventricular pacing is of concern just as it is during asynchronous ventricular pacing for ventricular tachycardia.[2] In our series very rapid ventricular tachycardia degenerating into ventricular fibrillation occurred in fewer than 1 percent of episodes (Table III). Nevertheless, if the technique is used cautiously, its benefits outweigh its risks. Laboratory and clinical experience shows that stimulation in the vulnerable period is less likely to cause ventricular fibrillation when unipolar cathodal stimulation is used at low levels of current output[24,25] and in a metabolically and hemodynamically compensated nonischemic ventricle.[26] We have usually used bipolar pacing for bursts of rapid ventricular pacing with temporary leads, but the implanted units were unipolar. Use of unipolar cathodal pacing with temporary electrodes and timing of the first stimulus of the bursts of rapid ventricular pacing to avoid the vulnerable period may further decrease the risks of ventricular fibrillation. Experimental observations indicate that rapid heart rates after acute myocardial infarction can be arrhythmogenic, perhaps as a result of increased nonuniformity of refractory periods.[27,28] Myocardial irritability is enhanced at rapid rates during ouabain toxicity.[29] Added caution is thus wise when bursts of pacing are used during states of acute myocardial infarction and digitalis toxicity, although we have used the technique successfully in both situations without an increased incidence of acceleration or ventricular fibrillation (Table IV).

Clinical applications: An implantable unipolar low output pacemaker delivering bursts of rapid ventricular pacing is appropriate when persistently recurring ventricular tachycardia responds best or only to pacing, without acceleration during many episodes over an extended period of time. The patient or family is thus provided with a mechanism for emergency conversion of ventricular tachycardia outside the hospital. When possible, however, the patient should go to the hospital before activating the pacemaker in case acceleration should occur. The family should be instructed in cardiopulmonary resuscitation.

Bursts of rapid ventricular pacing are useful in three clinical settings: (1) Acutely, if recurrent ventricular tachycardia has not been controlled by other means, bursts of pacing can minimize the need for direct current cardioversion. (2) During electrophysiologic studies in patients in more stable condition with recurrent ventricular tachycardia, bursts of pacing can immediately terminate an induced tachycardia, allowing serial testing of antiarrhythmic agents until a combination is found that protects the patient against ventricular tachycardia.[13–15] (3) In the rare patient whose tachycardia is not otherwise controlled, an implantable pacemaker is a useful option.

Treatment of 573 episodes of ventricular tachycardia with bursts of pacing has led to an appreciation of the benefits and risks of this technique. Bursts of rapid ventricular pacing represent a powerful addition to the therapies for recurrent ventricular tachycardia.

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Aortic Root Dissection Complicating Coronary Bypass Surgery

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Four cases are presented of aortic root dissection after aortocoronary bypass surgery in which the origin of the intimal tear was at or very near the aortic site of saphenous vein anastomosis. Two cases were documented at autopsy. In one of two cases diagnosed with aortography, the patient underwent surgical correction and survived. All patients had long-standing severe hypertensive cardiovascular disease or severe generalized atherosclerotic disease, or both. Clinical awareness of aortic dissection after coronary bypass surgery in this group of patients should make early diagnosis with successful surgical correction feasible.

Aortocoronary bypass surgery is an accepted surgical procedure for relief of angina pectoris refractory to medical treatment.[1,2] Recent reports[3,4] have also suggested prolonged survival with surgical management of left main coronary artery disease. Previously recognized complications of coronary bypass surgery[5,6] include postoperative infection, pulmonary embolism, pericarditis, pericardial tamponade[7] and myocardial infarction. Except for two cases recently reported,[8] dissecting aortic aneurysm initiated at the site of vein implant has not been recorded.

We report four well documented cases of aortic root dissection in which the intimal tear was at or very near the site of vein anastomosis. Three of our cases were recognized during the early postoperative course and one case several months later during follow-up study. One patient underwent aortographic confirmation and successful surgical correction of the dissection. All four patients had long-standing hypertensive cardiovascular disease or severe generalized atherosclerotic disease, or both. Awareness of this complication in this group of patients in the early postoperative period should encourage accurate diagnosis and prompt surgical correction of this potentially fatal complication.

Case Reports

Case 1

A 67 year old white man was admitted with progressive angina pectoris. He had had severe hypertensive cardiovascular disease for 22 years (diastolic blood pressure 90 to 140 mm Hg), with an episode of malignant hypertension in 1966. For 10 years he had had severe angina pectoris that required radioactive iodine ablation of thyroid function in 1966. Medications included propranolol (320 mg/day), isosorbide dinitrite, hydralazine, furosemide, digoxin and thyroxine. Physical examination revealed clinical myxedema. Blood pressure was 200/110 mm Hg, and a fourth heart sound was heard. Systolic bruits were present over the abdominal aorta and both femoral arteries; popliteal and pedal pulses were absent. Chest roentgenography revealed mild left ventricular enlargement. Electrocardiography disclosed normal sinus rhythm, old inferior infarction and left ventricular hypertrophy. The patient underwent cardiac catheterization and surgery. Cardiac catheterization disclosed severe triple vessel coronary artery disease with subtotal stenosis of the left main artery. A bypass graft to the left anterior descending artery was performed at Emory University Hospital.

During the first postoperative day because of markedly fluctuating hypertension (diastolic pressure 135 mm Hg) the patient was treated with diazoxide,

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FIGURE 1. Case 1. Ascending aorta showing sites of vein anastomosis **(white arrow)** and aortic tear **(black arrow).**

propranolol (20 to 40 mg every 6 hours) and hydralazine. On the fifth postoperative day he complained of precordial pain radiating to the posterior cervical area. On the eighth postoperative day the pain recurred, blood pressure was 200/120 mm Hg and the patient became pale and diaphoretic. The neck veins were distended, and a grade 2/6 murmur of aortic regurgitation was noted. Pericardiocentesis of 200 cc of bloody fluid provided temporary relief, but the patient subsequently had a cardiac arrest and died.

Autopsy revealed a 1.5 cm tear in the aortic root near the site of vein graft anastomosis (Fig. 1) with aortic dissection and rupture into the pericardium. There was severe generalized atherosclerosis and right renal arterial stenosis. Histologic examination of the aorta revealed no cystic medial necrosis but severe intimal atheroma.

Comment: This patient had long-standing hypertension and severe peripheral atherosclerosis. The postoperative course was complicated by widely fluctuating hypertension. Aortic dissection with the tear near the site of the vein implant occurred with severe chest pain, aortic regurgitation, cardiac tamponade and death. Severe generalized atherosclerosis and no medial disease of the aorta were documented at autopsy.

Case 2

A 51 year old white man with angina pectoris refractory to medical treatment was admitted for cardiac catheterization. The patient had a 10 year history of hypertension (diastolic blood pressure 90 to 130 mm Hg). Angina pectoris of 5 years' duration had worsened significantly in the previous 3 months despite treatment with propranolol (160 mg/day) and isosorbide dinitrite. Physical examination revealed a blood pressure of 210/120 mm Hg, an apex impulse displaced 1 cm lateral to the mid-clavicular line, abnormal S_3 and S_4 heart sounds and a 2/6 holosystolic murmur at the apex. The electrocardiogram revealed left ventricular hypertrophy, and the chest roentgenogram disclosed mild left ventricular enlargement. An exercise tolerance test revealed 4 mm S-T depression at 1 1/2 minutes of stage I of the standard Bruce protocol; cardiac catheterization disclosed severe triple vessel coronary artery disease. The patient underwent double aortocoronary bypass graft surgery at the Emory University Hospital.

On the first postoperative day the patient had marked hypertension (245/140 mm Hg) that responded initially to diazoxide. On the second postoperative day widely fluctuating hypertension was treated with propranolol (40 mg every 6 hours), hydralazine and methyldopa. On the eighth postoperative day the patient had a sudden onset of severe precordial pain and diaphoresis and became pulseless; attempts at resuscitation were unsuccessful.

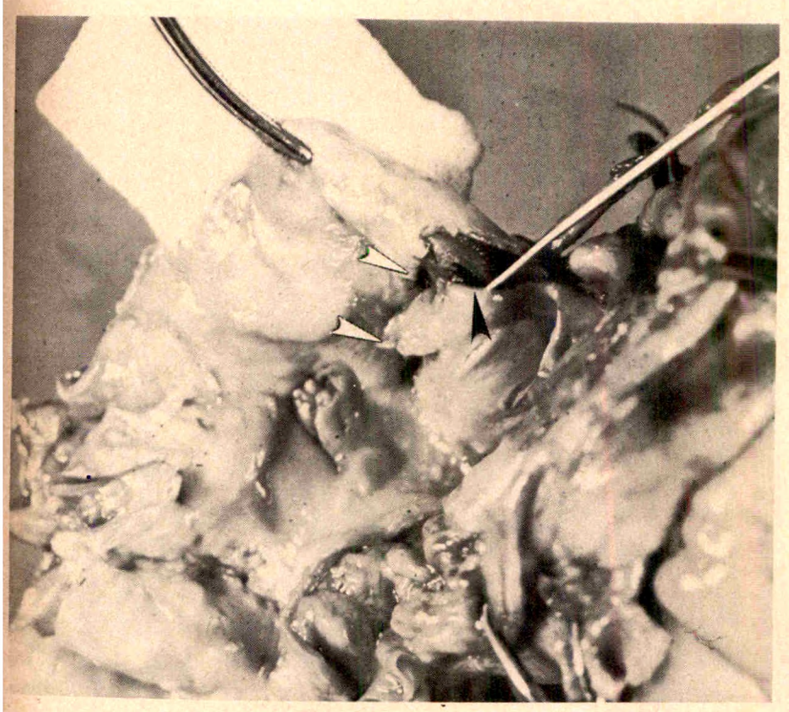

FIGURE 2. Case 2. Ascending aorta showing sites of vein anastomosis **(white arrows)** and aortic tear **(black arrow).**

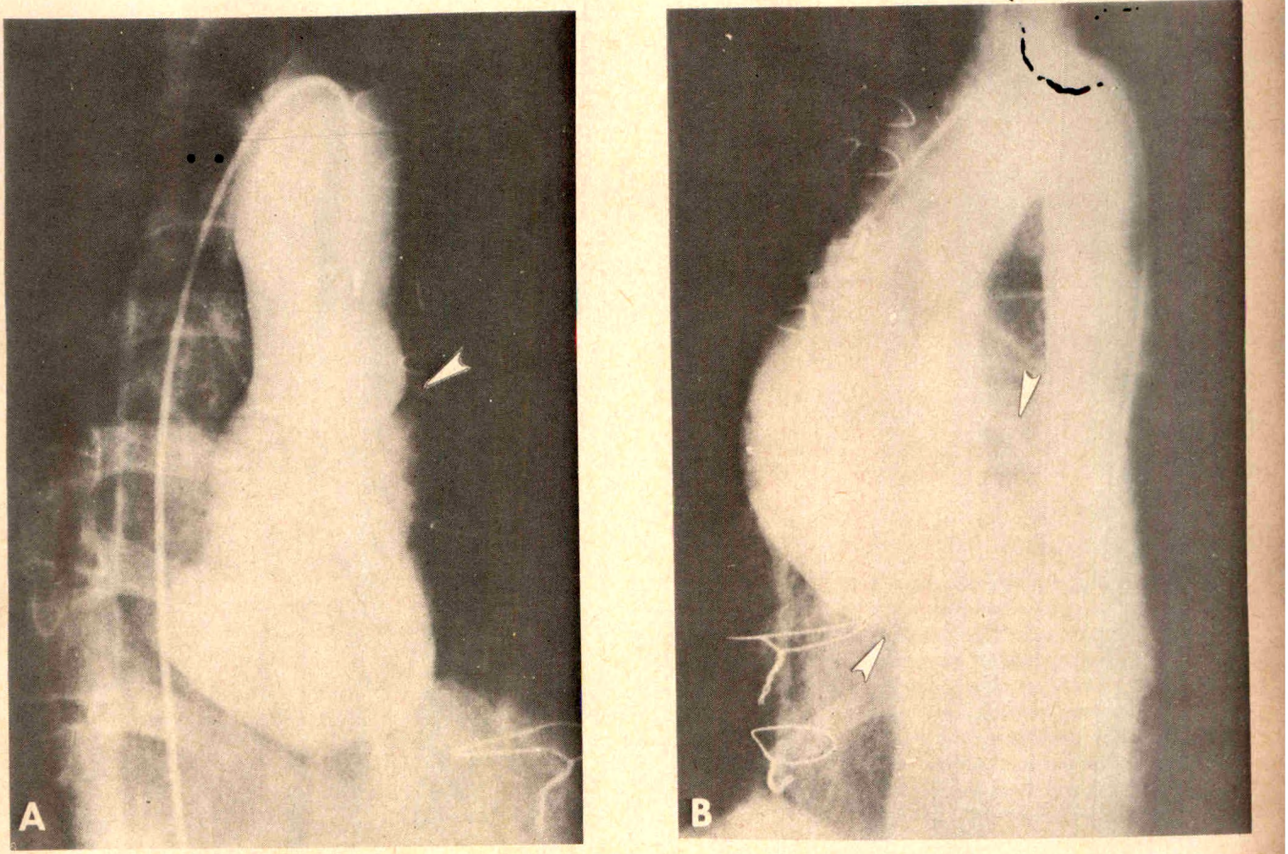

FIGURE 3. Case 3. Aortogram. **A,** right anterior oblique view demonstrating intimal tear **(arrow)** near vein implant site. **B,** left anterior oblique view demonstrating saphenous vein **(upper arrow)** and proximal intimal tear **(lower arrow).**

Autopsy revealed a 1.5 cm intimal tear in the ascending aorta (Fig. 2) continuous with the site of anastomosis of the second vein graft. There was dissection of the intima and media with perforation of the adventitia and associated hemopericardium. There was severe generalized atherosclerosis. Histologic study of the aorta revealed no cystic medial necrosis but severe intimal atheroma.

Comment: This patient with long-standing severe hypertension and severe generalized atherosclerosis documented at autopsy had the sudden onset on the eighth postoperative day of severe precordial chest pain and diaphoresis; he died as a result of dissection of the aorta with perforation of the aorta into the pericardium and cardiac tamponade.

Case 3

A 50 year old white man with severe angina pectoris was admitted for cardiac catheterization. The patient was known to have had severe hypertension for 10 years (diastolic pressure 90 to 120 mm Hg) and renal arterial stenosis in 1973. Angina pectoris of 3 years' duration had become progressively worse during the previous 3 months although he was treated with propranolol (320 mg/day), isosorbide dinitrite, nitrol ointment and digoxin. Physical examination revealed a blood pressure of 130/90 mm Hg. There were a systolic bruit over the left carotid artery and bruits over the abdominal aorta and both femoral arteries. Popliteal and pedal pulses were absent; there was a fourth heart sound. The electrocardiogram revealed old inferior myocardial infarction and left ventricular hypertrophy; the chest roentgenogram was normal. Cardiac catheterization disclosed severe triple vessel and left main coronary artery disease. The patient underwent triple aortocoronary bypass surgery at the University of Alabama Hospital.

The immediate postoperative course was complicated by severe hypertension (diastolic pressure 125 mm Hg), and the patient was treated initially with diazoxide and later with methyldopa. On the eighth postoperative day he was noted to have a grade 3/6 diastolic regurgitant murmur at the lower left sternal border. The chest roentgenogram revealed a dilated ascending aorta, slightly enlarged cardiac silhouette and interstitial pulmonary edema. The patient responded to treatment for heart failure; blood cultures were negative. The aortogram (Fig. 3) documented a dissecting aneurysm limited to the ascending aorta. The patient underwent successful repair of his dissecting aneurysm, with replacement of the ascending aorta with a Dacron® tube and reanastomosis of the proximal ends of the saphenous veins. Postoperatively, he has returned home and does not have angina pectoris or aortic regurgitation.

Comment: This patient with long-standing hypertension and severe peripheral atherosclerosis underwent aortocoronary bypass surgery. On the eighth postoperative day he had aortic regurgitation of new onset and a dilated ascending aorta, revealed with roentgenography. An aortogram documented the aortic dissection, and the patient underwent successful surgical repair of his dissecting aneurysm.

Case 4

A 67 year old man presented with angina pectoris of 3 years' duration that had become progressively severe during the

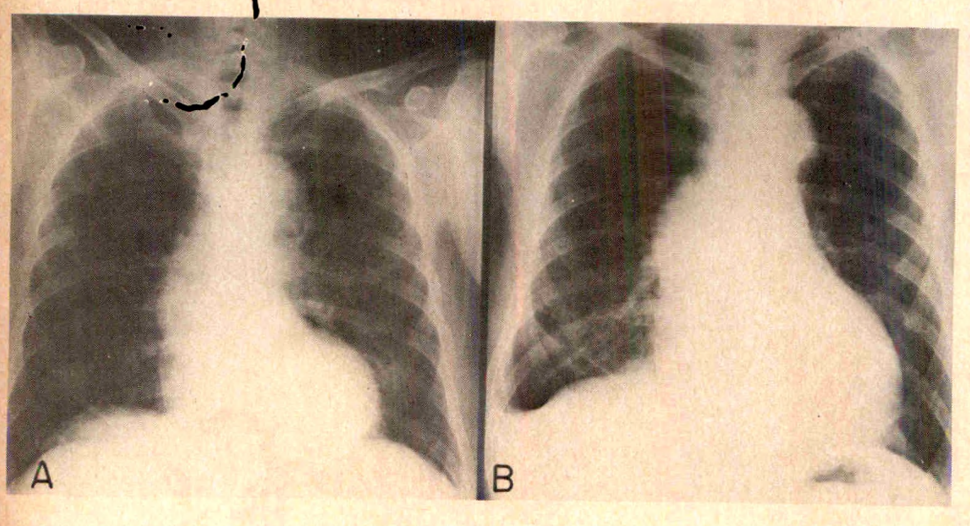

FIGURE 4. Case 4. Chest roentgenograms. **A,** 6 weeks after surgery showing mild dilatation of the ascending aorta. **B,** 10 months after surgery revealing marked dilatation of the ascending aorta, cardiomegaly and right pleural effusion.

previous 3 weeks, causing daily pain on rest. He had had hypertension for 10 years (diastolic pressure 90 to 100 mm Hg). On physical examination the blood pressure was 140/85 mm Hg. An abnormal third heart sound was heard in the left lateral decubitus position. There were no murmurs, and peripheral pulses were normal. The electrocardiogram revealed normal sinus rhythm and an old anterior infarction. The size and shape of the cardiac silhouette were normal on chest roentgenography, and there was no dilatation of the ascending aorta. Coronary arteriography demonstrated 60 percent luminal narrowing of the left main coronary artery and 60 to 80 percent lesions of the left anterior descending, circumflex and right coronary arteries.

At operation (York Hospital, Pennsylvania), three aortocoronary grafts were placed without difficulty. The immediate postoperative course was complicated by three episodes of bleeding requiring exploration. In addition, diazoxide was administered for the control of hypertension (mean arterial pressure 110 to 120 mm Hg). On evaluation 6 weeks after discharge from the hospital the patient was doing well and had no angina on moderate activity and no murmurs. The chest roentgenogram at that time revealed mild dilatation of the ascending aorta (Fig. 4A).

Ten months after operation, the patient presented with a 2 month history of progressive dyspnea and easy fatigability but no angina pectoris. Physical examination revealed blood pressure of 130/75 mm Hg, a laterally displaced and sustained apex impulse, abnormal third and fourth heart sounds and a grade 2/6 diastolic decrescendo murmur at the lower left sternal border. The chest roentgenogram (Fig. 4B) revealed cardiomegaly, marked dilatation of the ascending aorta and interstitial edema. The aortogram demonstrated a large aneurysm limited to the ascending aorta and an intimal flap just above the aortic cusps. Surgery is planned.

Comment: This patient, like the first three, had a history of hypertension (although less severe), and diazoxide was administered during the immediate postoperative period. However, he did not have evidence of peripheral vascular disease. Presumably dissection occurred at the time of aortocoronary bypass surgery but did not become apparent until months later, when severe aortic regurgitation and heart failure developed. Awareness of this complication from our experience with the three previous cases prompted early aortography and recommendation for surgical correction.

Discussion

Previous reports[9,10] of dissecting aneurysm during cardiopulmonary bypass include aortoiliac retrograde dissection from the site of femoral cannulation to the ascending aorta. Also reported[11] was a false aneurysm of the ascending aorta after aortic valve replacement. Dissection of the aorta has occurred as a result of aortic cannulation[12] and after clamping of an extensively atheromatous aorta.[13] In two patients recently reported[8] to have dissection at the site of aortic anastomosis after saphenous vein bypass surgery pathologic examination was not performed, but atherosclerosis was noted at surgery.

Predisposing and provocative factors: A history of hypertension is frequently present in cases of aortic dissection.[14] Our four patients had documented long-standing severe hypertensive cardiovascular disease. Braunstein[15] thought that advanced atherosclerotic lesions predispose to aortic dissection. Generalized atherosclerosis was documented in all four of our patients. Patient 3 had obstructive ileofemoral disease documented angiographically, and Patient 1 had both peripheral atherosclerosis and hypertension and hypothyroidism. The combination of the latter two problems is said to predispose to aortic dissection.[16]

Dissecting aneurysm begins with injury to the diseased aortic wall followed by intramural hemorrhage.[17] This hemorrhage forms an intramural hematoma that may be either preceded or followed by an intimal tear. The progression of the hematoma determines the extent of dissection.

Long-standing severe atherosclerosis and hypertensive disease established weakness in the aortic wall of our patients. Cystic medial necrosis was not present in the two aortas examined histologically, but severe atheromatous disease of the intima was present. The obligate clamping to the aorta at the site of vein graft anastomosis appears to be sufficiently traumatic to initiate hematoma formation and cause the intimal tear

at or near the site of anastomosis, as seen in our patients.

Increased rate of development of pressure (dP/dt) has been shown by Prokop et al.[18] to be highly undesirable in cases of aortic dissection. The use of diazoxide in all four patients during the early postoperative course may also have contributed to extension of the dissecting aneurysm by a reflex catechol-mediated increase in dP/dt of the cardiac stroke volume.[19]

Clinical signs: The patient with dissected aneurysm will present any of several well recognized findings and complications. Aortic regurgitation, a frequent occurrence in aortic dissections (23 to 25 percent),[15,20] was noted in three of our patients as the earliest clinical sign of the underlying diagnosis. Rupture of the aorta with ensuing cardiac tamponade, a well recognized complication of aortic dissection,[15,20] resulted in the death of two of our patients. Severe chest pain is a frequent subjective complaint in aortic dissection[15,20] and was present in two of our four patients.

Surgical precautions, prevention and treatment: Although the four operations were performed by four different surgeons in three institutions, certain elements of surgical trauma were constant. In all patients the proximal vein graft was sutured into the ascending aorta within the confines of a partial occlusion vascular clamp. The clamp was applied to the aorta while either normal cardiac output or partial cardiopulmonary bypass was maintained; that is, there was a significant pressure (normal or hypertensive) in the aorta. Realizing that delayed dissection occurs in the setting of hypertension and generalized atherosclerosis, the surgeon in such cases should modify the operative technique to permit application of relatively atraumatic clamps to the aorta while the patient is rendered temporarily hypotensive by the administration of drugs or by reduction in pump flow if the patient is on partial bypass. In extreme cases of atherosclerosis of the ascending aorta, a totally occlusive clamp should be applied to the aorta just proximal to the site of arterial cannulation while the patient is hypotensive, and the grafts should then be sutured into the aorta, which has totally collapsed.

The patient with long-standing severe hypertension or severe atherosclerotic peripheral vascular disease, or both, is at risk of dissecting aneurysm at the site of vein anastomosis to the ascending aorta. Although clamping of the aorta cannot be avoided, the number of applications should be kept to an absolute minimum, and the aortic pressure should be temporarily reduced to a hypotensive range while the clamp is applied. During the postoperative period the possibility of delayed dissection in such patients should be kept in mind. If signs or symptoms compatible with dissection occur, characteristically on the 6th to 8th day, prompt diagnosis and treatment should be undertaken. This complication must be considered not only in the early postoperative period but also during follow-up studies. The findings of dilatation of the ascending aorta, congestive heart failure or aortic regurgitation of new onset, alone or in combination, should alert one to the occurrence of this complication. Cardiac tamponade and chest pain may also accompany postoperative dissection. Awareness of this complication can provide the opportunity for diagnostic aortography and surgical correction.

Acknowledgment

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EDITORIAL

Origin of the Second Heart Sound: Clinical Relevance of New Observations

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In this day of emphasis upon clinical relevance, and the emphasis placed by governmental granting agencies upon directly applicable research, one wonders if there is any value in detailed investigations related to the mechanism of production of the second heart sound. Points of infinitesimal accuracy are debated, such as whether the second sound starts milliseconds before or after total semilunar valve closure, or whether vibration of nonvalve structures participates in the closure sound. We believe that these issues are important and clinically relevant. Specifically, recent information related to the origin of the second sound permits one to interpret clinical auscultatory phenomena that previously were puzzling and sometimes seemingly paradoxical.

In 1915 Wiggers[1] suggested that there is silent approximation of the semilunar valves and that after-vibrations of the closed valves and the column of blood produce the second heart sound. In 1938 Lewis and Dock[2] indicated that the second sound is of purely valve origin and excluded the myocardium as a structure contributing to the heart sounds. Studies a century earlier by Rouanet[3] indicated that heart sounds (in this case the first sound) could be caused in a fashion similar to sound produced by any membrane as it passes "from flaccidity to tension suddenly." In recent years, many factors have been postulated to contribute to sound production although experimental evidence has been limited in some instances.

Rushmer[4] related the origin of the second sound to oscillations in the arterial and ventricular cavities initiated by the momentum of backward-moving blood, which causes stretch and subsequent recoil of the valve. Coleman[5] attributed the second sound to the sudden snapping together of the corpora arantii, which he postulated provides sufficient energy to vibrate the tensed leaflets. Piemme et al.[6] suggested that the main vibrations of the second sound are related to the magnitude of deceleration of blood during the latter part of ventricular systole. Luisada et al.[7] suggested that several factors contribute to the second sound, including eddies that precede semilunar closure, closure of the semilunar valves and opening of the atrioventricular (A-V) valves. They also suggested[8] that the walls of the ascending aorta, the outflow tract of the ventricle and blood itself as well as the aortic valve constitute the vibrant mass that results in a short series of vibrations recognized as the second sound.

Vibrations of closed semilunar valve as cause of the second heart sound: Investigations in our laboratory[9] indicate that the valve in fact closes silently and that vibrations of the closed valve are the source of the second sound. During early diastole the semilunar valve, being thin, compliant and tense, can be considered to act as a stretched circular membrane. When such a membrane is set into motion by a driving force, it generates compression and rarefaction of the ambient fluid that result in transient pressure changes productive of audible sound. Distension of the tensed leaflets toward the ventricle causes compression of the blood within the ventricle and rarefaction of the blood within the aorta (or pulmonary artery). Recoil of the valve toward the aorta (or pulmonary artery) causes a relative rarefaction of the blood within the ventricle and compression within the aorta. Thus, after silent closure, the valve vibrates as a diaphragm, producing pressure changes that are recognized as sound.[9]

This concept of the origin of the second sound is compatible with the view that valve vibration is primary in its production. A point of critical distinction is that the force productive of valve vibration would seem to be the pressure gradient that exists between the aorta and the ventricle just after valve closure and not the reversed flow or the deceleration of flow. This difference is important in the development of a theory that is compatible with standard concepts of fluid dynamics. Many of the characteristics of the second sound can be explained by considering the diastolic vibrations of the valve as the source of the second sound, and by con-

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sidering the pressure gradient that develops between the ventricle and arterial chamber as the driving force productive of the vibrations. Numerous auscultatory phenomena now can be explained by further consideration of this concept.

Experimental evidence and theoretical analysis: To substantiate this concept of production of the second sound, two principal avenues of investigation were conducted. First, semilunar valve dynamics were studied in vitro, in animals and in human subjects.[9] The relation of sound to pressure and flow was studied with special emphasis upon the high fidelity recording of intraarterial pressure and intraarterial sound in order to perceive better any minor fluctuations of pressure and sound that may occur. The use of an in vitro model of the cardiovascular system in which high speed motion pictures could relate valve motion and the position of the valve to hemodynamic events was particularly revealing. Second, a mathematical model of the motion of the semilunar valve in early diastole was formulated (Blick EF, Sabbah HN, Stein PD, unpublished observations). The model was derived on the basis of membrane vibration analysis and theories of sound production. The combination of both the experimental evidence and the theoretical analysis, some of which we have confirmed with studies in animals, gave sufficient evidence to support this concept of sound production.

The following experimental results were observed[9–12]: (1) The onset of the second heart sound began after total coaptation of the semilunar leaflets. This was shown with mounted porcine valves in vitro using high speed motion pictures at 2,000 frames/sec in combination with a sound transducer attached to an oscilloscope. (2) These same movies indicated asymmetric closure of the leaflets. A sequential approximation of the margins of the cusps occurred, starting peripherally and moving centrally. Some cusps were completely closed; others were still part open. This nonsimultaneous contact of the valve margins indicated that impact would occur with minimal energy, which in all likelihood is not sufficient to cause valve vibrations. (3) The amplitude of the second sound was shown to be independent of forward or retrograde flow. (4) Vibrations of the semilunar valve after closure were shown to occur in vitro, using 2,000 frames/sec cine film. Analyses of the rate and extent of valve motion from these motion pictures (Sabbah HN, Stein PD, unpublished observations) indicated that this motion may contain the entire frequency spectrum of the second sound previously observed by others. (5) The deflection of the primary vibration and secondary vibration of sound recorded within the ventricle are in a direction opposite to those of the deflections recorded within the aorta (or pulmonary artery). This indicates that, as compression occurs within the ventricle, rarefaction occurs within the arterial cavity, and vice versa. (6) The first major deflection of sound recorded from within the ventricle is invariably inscribed in the direction produced by compression. One would expect this, since the initial motion of the valve after semilunar closure is toward the outflow tract of the left ventricle. Simultaneously, the first major deflection of sound recorded from within the aorta is inscribed in the direction caused by rarefaction. (7) Close inspection of aortic, pulmonary and ventricular pressure recordings in both man and laboratory animals shows during early diastole the presence of transient changes of pressure that are coincident with the components of the second sound. These pressure transients appear to result from the same compression and rarefaction generated in the ventricles and their corresponding arterial chambers as a result of the vibrations of the semilunar valves.

Analysis of membrane vibration can be used to describe the valve motion if one considers the closed semilunar valve during early diastole to act as a vibrating tensed membrane driven by a diastolic pressure gradient. From the derived equations, one can explain and predict clinical auscultatory phenomena related to the amplitude of the second sound. Sound pressure produced by a vibrating membrane relates primarily to the rate of deflection of the membrane; that is, the amplitude of sound relates to the velocity of the valve as it distends toward the ventricle and recoils toward the aorta. Therefore, if an equation could be derived that described the rate of deflection of the valve in terms of the factors that affect its motion, the variables that affect the intensity of sound would be apparent. The solution of such an equation of motion is complex, because the distensibility of valve tissue varies with the extent to which the valve is stretched. A partial solution, nevertheless, shows several features that explain previously unexplained clinical observations*: (1) The amplitude and rate of valve distension produced by the early diastolic pressure gradient between the aorta and ventricle are related to the rate of change of this pressure gradient. Others[13] have found this to be true empirically and we[11] showed it prospectively with this analysis in mind. The rate of change of the diastolic pressure gradient relates closely to the rate of isovolumic relaxation.[11] Consequently, the amplitude of the aortic closure sound relates to the rate of isovolumic relaxation and, by implication, the amplitude of the second sound relates to ventricular performance. This would explain the tictac rhythm and reduced second sound sometimes heard in normotensive patients after an acute myocardial infarction or during heart failure.[14]

Clinical Relevance

Aortic stenosis: Both the modulus of elasticity of the valve and its mass are shown in the equation of valve motion to affect the extent and rate of valve deflection. This has particular clinical relevance in regard to the interpretation of auscultatory findings in aortic stenosis (Sabbah HN, Blick EF, Stein PD, unpublished observations). In acquired calcific aortic stenosis, the valve is thickened and stiffened. Thus, because of its increased mass and decreased flexibility, its ability to vibrate during diastole is diminished. A reduced second sound would therefore be expected with such a valve. In contradistinction, in children with congenital aortic stenosis the leaflets are thin and flexible. Because there is no impediment to diastolic vibration of the closed cusps, a second sound of normal intensity would be expected and it, of course, occurs. The diminished second sound in calcific aortic stenosis, and its paradoxical continued presence in congenital aortic stenosis, is therefore explained on the basis of this membrane concept of sound production (Sabbah HN, Blick EF, Stein PD, unpublished observations).

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* Unpublished observations. Membrane analysis made by Edward F. Blick, PhD of the University of Oklahoma School of Aerospace, Mechanical and Nuclear Engineering.

Aortic insufficiency: In aortic insufficiency, firm approximation of all portions of the cusps does not occur. In such cases, the ability of the valve to tense and vibrate is reduced. On the basis of the membrane origin of the second sound, the amplitude of the second sound would be expected to be diminished. We[15] have consistently observed a diminished aortic component of the second sound in intraarterial recordings of patients with aortic regurgitation although the published data vary.

Intensity of pulmonary versus aortic component of the second sound: An explanation of the decreased intensity of the pulmonary component of the second sound relative to the aortic component is found by consideration of the factors that affect diastolic vibration of the valves. The rate of isovolumic diastolic relaxation of the right ventricle is lower than that of the left ventricle. Therefore, the rate of change of the diastolic pressure gradient between the right ventricle and pulmonary artery is lower and consequently a lower pulmonary closure sound is produced. This is partially compensated for, however, because the pulmonary valve is larger in diameter and thinner than the aortic valve. Membrane vibration analysis shows that the intensity of sound is dependent upon the diameter of the vibrating membrane, in this case the valve. In addition, because the pulmonary valve is thinner than the aortic valve it is likely to be more distensible.

Sound transients: The low amplitude sound vibrations during the last portion of the second sound, termed sound transients, have been postulated to represent sound induced by arterial vibrations and the opening of the A-V valves.[16] However, studies of mounted valves in vitro showed sound transients; yet the in vitro model of the cardiovascular system contained no structure other than the valve that was able to vibrate. Therefore, it is clear that the valve itself can produce the sound transients. It would seem that these sound transients indicate the late low velocity and low amplitude deflections of the valve just before diastolic vibration ceases. This observation is compatible with the equations of valve motion.

Other factors affecting intensity of second sound: Other factors, in addition to those described, that were not previously recognized to relate to the intensity of the second sound are shown by membrane vibration analysis to affect sound amplitude (Blick EF, Sabbah HN, Stein PD, unpublished observations). These include the density of the blood, the frequency of valve vibration, the volume and geometry of the ventricle, the coefficient of sound absorption of the ventricular wall and the damping force coefficient. The sound absorption of the ventricular wall perhaps may relate to the thickness of the ventricular wall and to the presence of scar. The damping force coefficient relates primarily to the viscosity of the blood, which varies greatly in patients, particularly with varying hematocrit levels.

Conclusion

It is clinically useful to recognize that the second heart sound is caused by vibration of the closed semilunar leaflets just after silent coaptation. If one conceives of the closed valve as a vibrating stretched membrane, then one can recognize the factors that affect diastolic valve vibration and ultimately affect the intensity of sound. These include the rate at which the driving pressure develops (the rate of change of the diastolic pressure gradient), the flexibility of the valve, its mass and diameter, the density and viscosity of the blood, the frequency of valve vibration, the coefficient of sound absorption of the ventricular walls and the geometry of the ventricle. These factors affect the production of the second sound. They are independent of the multiple factors that affect the transmission of sound. Clearly, therefore, the clinical interpretation of the intensity of the second sound is affected by a complex array of variables. In spite of this, understanding of the physiology of production of the second sound permits an understanding of numerous previously unexplained clinical observations. Further analyses of this nature will continue to increase our understanding of auscultatory phenomena.

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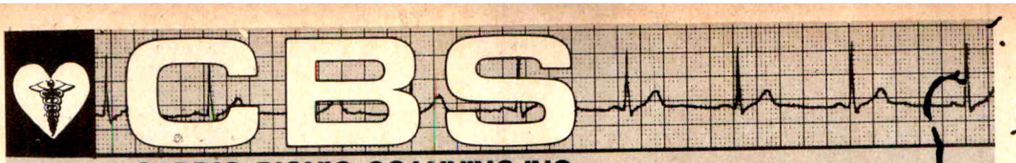

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PATIENT _____ DATE 10/10/77 - 10/11/77

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PHYSICIAN _____

QUALITY OF RECORDING	PATIENT DIARY SUBMITTED	SYMPTOMS REPORTED	CALIBRATIONS
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HOUR	VENTRICULAR * ECTOPIC BEATS	PVC's * PER 1000 BEATS	SUPRAVENTRICULAR ECTOPIC BEATS	ST-T CHANGES IN MM	TOTAL BEATS	RATE
4-5pm	5	3	0	-0.5		62
5-6	7	4	21	0		68
6-7	16	7	10	-1.0	total	66
7-8	12	5	1	-0.5	beats:	68
8-9	24	10	5	0	87088	62
9-10	18	8	2	0		65
10-11	30	11	3	0		61
11-12	15	7	3	**		58
12-1 am	35	13	4	**		50
1-2	61	20	0	0		57
2-3	20	9	2	-0.5		59
3-4	19	8	4	+1,0		51
4-5	11	5	2	+1.5		49
5-6	3	10	5	**		52
6-7	40	16	1	-1.0		57
7-8	19	8	1	-1.0		70
8-9	19	28	0	-0.5		77
9-10	68	29	5	-1.0		69
10-11	25	10	1	-0.5		68
11-12	18	8	1	-1.0		64
12-1 pm	7	4	0	-0.5		74
1-2	13	6	3	-0.5		66
2-3	2	2	12	-0.5		70

HEART RATE

MAXIMUM OF *159 BEATS PER MINUTE AT 12:24am MINIMUM OF **30 BEATS PER MINUTE AT 11:53am

*starts & ends abruptly, 3.8 sec. longest R-R interval @ 4:12pm, 3.04 sec.

**see writeouts.

Peter L Goodfriend

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To know more about why CBS is the only total scan and supply service clip the coupon and mail it today. If you believe in the importance of Holter monitoring then you owe it to yourself and your patients to look into Cardio-Bionic-Scanning.

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EXERCISE TESTING BASICS:

Stress testing is rapidly becoming a standard diagnostic tool. But setting up your own stress testing unit can be costly. The equipment shown here will give you a basic system, flexible enough to build on for years to come.

Select a treadmill that will last. The treadmill is the basic workhorse of the system. It has to be durable. For 16 years, Quinton treadmills have been the standard in research centers, heart clinics and everyday practice.

We build seven models. All feature endless nylon belts for extra long service life, aircraft type honeycombed aluminum decks, lifetime lubricated bearings and heavy duty AC motors with "no jerk" speed control.

Quinton treadmills offer variable speed and elevation with metered readouts for both.

Treadmill Model 18-54

Select a practical multi-channel ECG monitor. Quinton offers a variety of ECG monitors. Our Model 623 two-channel unit has the versatility of multiple channel monitoring without the expense of three channel systems.

The Quinton Model 623 gives you pushbutton lead selection and lets you display and record any two leads simultaneously. With the QRS Sync feature, each consecutive QRS complex can be expanded to the full width of the screen, making even small changes obvious immediately.

No battery packs are required with the 623 and the internal calibration system not only checks the recorder before you conduct a test, it also checks the oscilloscope, patient cables and heart rate meter to assure you of total system accuracy.

Model 623 ECG Monitoring System

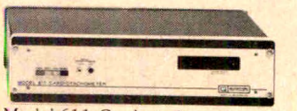
Build the system as your practice grows. Quinton offers a number of special purpose units which will expand the system's capabilities as your needs grow.

A Quinton programmer allows you to concentrate on the monitor and the patient while the test progresses automatically.

Treadmill Programmer

The Quinton ECG Data Computer digitally displays the heartrate, S-T level and S-T slope. It averages the signal to help you "see through" noisy ECG, and it records heartrate, S-T changes, arrhythmias and 20 beat ECG averages.

Model 740 ECG Data Computer

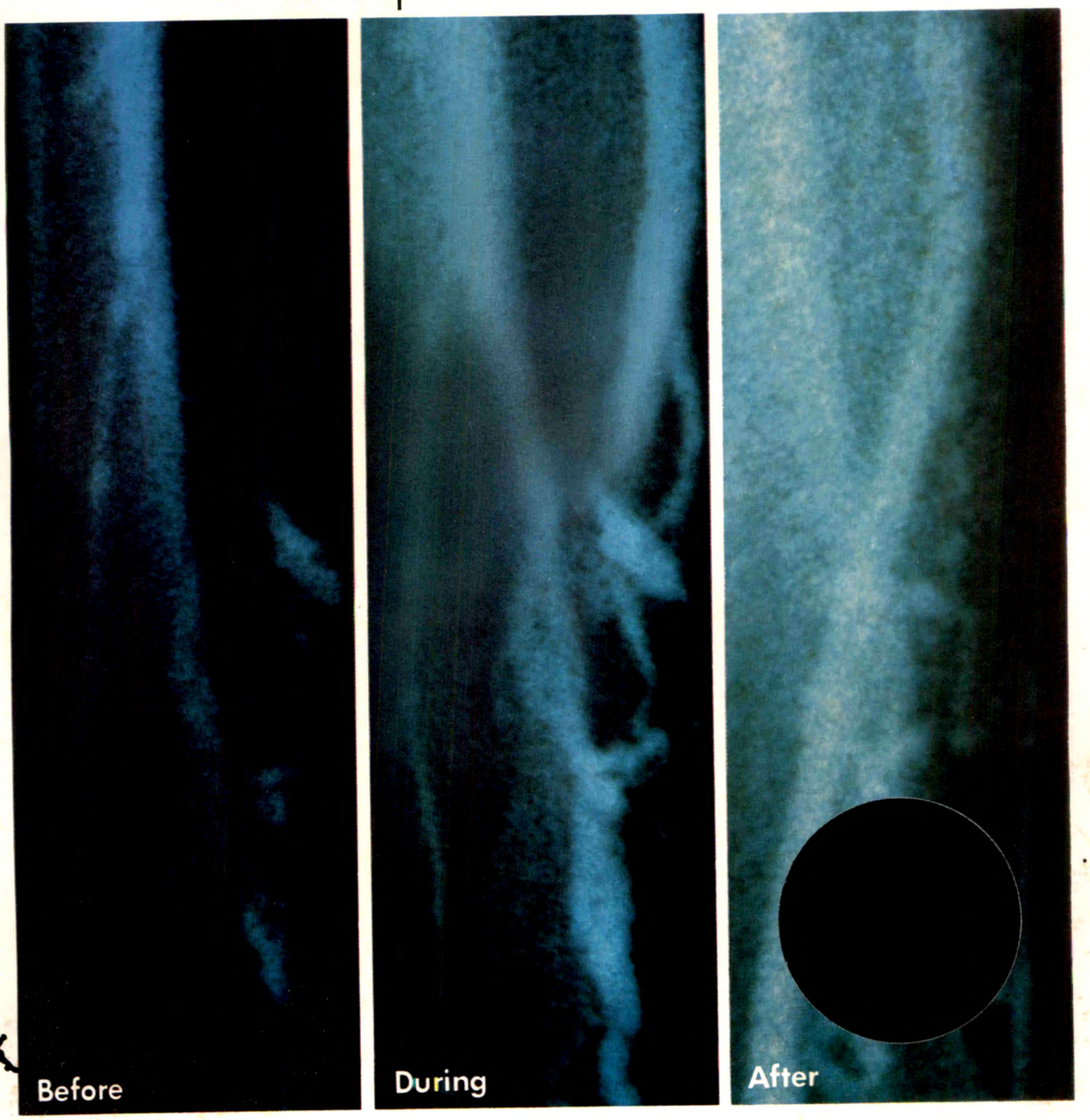


Model 611 Cardiotachometer

The Quinton cardiotachometer computes and digitally displays heartrate on an instantaneous, beat-by-beat basis. For details on all these products, contact Quinton Instrument Co., Dept. E16, 2121 Terry Avenue, Seattle, Washington 98121. Call 206/223-7373 or dial toll free 800-426-0538. **QUINTON**

You are looking at the dissolution of a thrombus.

Time required: 72 hours or less.



Introducing the first thrombolytic agent
for objectively diagnosed deep venous thrombi
and acute massive pulmonary emboli.

Hoechst-Roussel Pharmaceuticals Inc.

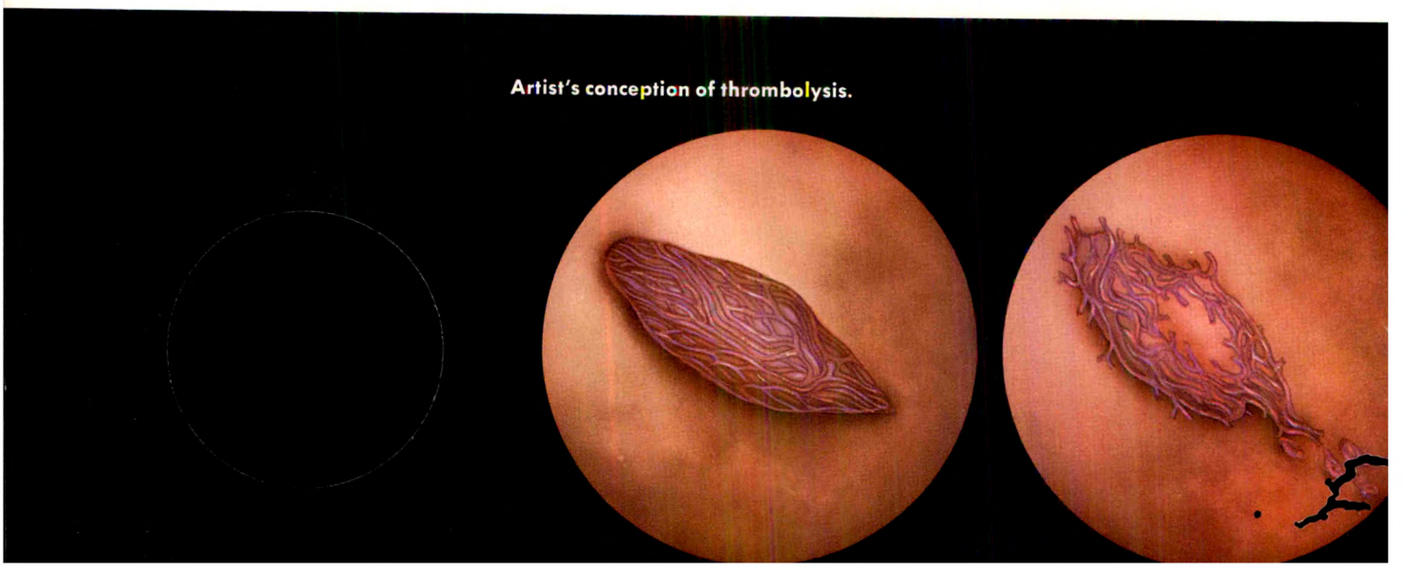
Announces

Streptase®

(streptokinase) I.V.

Now... a new alternative to surgery...

- **avoids the risks associated with thrombectomy.**
- **reduces the need for high-risk pulmonary embolectomy.**



To lyse venous thrombi and pulmonary emboli—intravenous Streptase®(streptokinase). Anticoagulant therapy is given following Streptase to prevent rethrombosis.

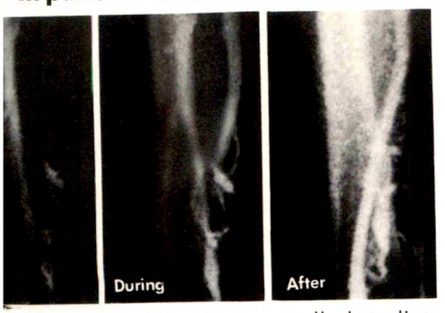
Now physicians have available a medical therapy for the early clearance of deep venous thrombi that is preferable to thrombectomy because it may preserve valvular function and avoid chronic stasis, although long-term benefits have not been established. And acute massive pulmonary emboli may be cleared without high-risk embolectomy.

A unique mode of action

New Streptase is the highly purified form of streptokinase, a bacterial protein derived from β-hemolytic streptococci. It combines with plasminogen to form an activator complex that converts residual plasminogen into the proteolytic enzyme plasmin. Plasmin hydrolyzes fibrin into polypeptides.

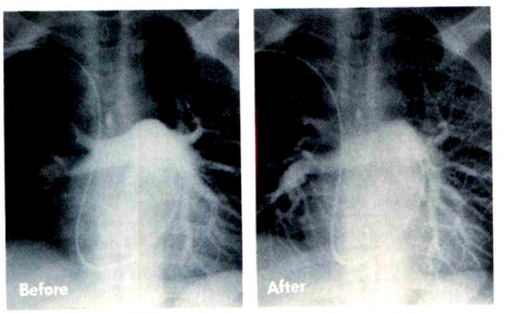
High rate of clinical success demonstrated by angiography:

In patients with venous thrombosis



In comparative controlled studies of 78 patients with venous thrombosis, Streptase produced complete or significant clearing of the thrombosis in 54% of patients while only 7% on conventional heparin therapy showed similar results.

In patients with pulmonary embolism



In studies of 124 patients with pulmonary embolism, complete or significant clearing was seen in 66% of the patients on Streptase but in only 11% of the heparin-treated patients.

Table I
Comparative angiographic results during controlled investigations*

Results	Venous Thrombosis		Pulmonary Embolism	
	Streptase (37 patients)	Heparin (41 patients)	Streptase (36 patients)	Heparin (88 patients)
Complete clearing	22%	5%	22%	5%
Significant, but incomplete, clearing	32%	2%	44%	6%
Minimal clearing	21%	20%	20%	43%
No change	22%	66%	14%	35%
Worse	3%	7%	0%	11%

In most cases, clearance was achieved in 72 hours or less.

For best results, Streptase should be used within 2 weeks after onset of venous thrombosis symptoms and within 5 days after onset of pulmonary embolism symptoms. Please see last page of this advertisement for a brief summary of prescribing information.

*Data on file and available on request from Hoechst-Roussel Pharmaceuticals Incorporated. Pulmonary embolism data include those taken from National Heart and Lung Institute study.

Thrombosis and thrombolysis information available

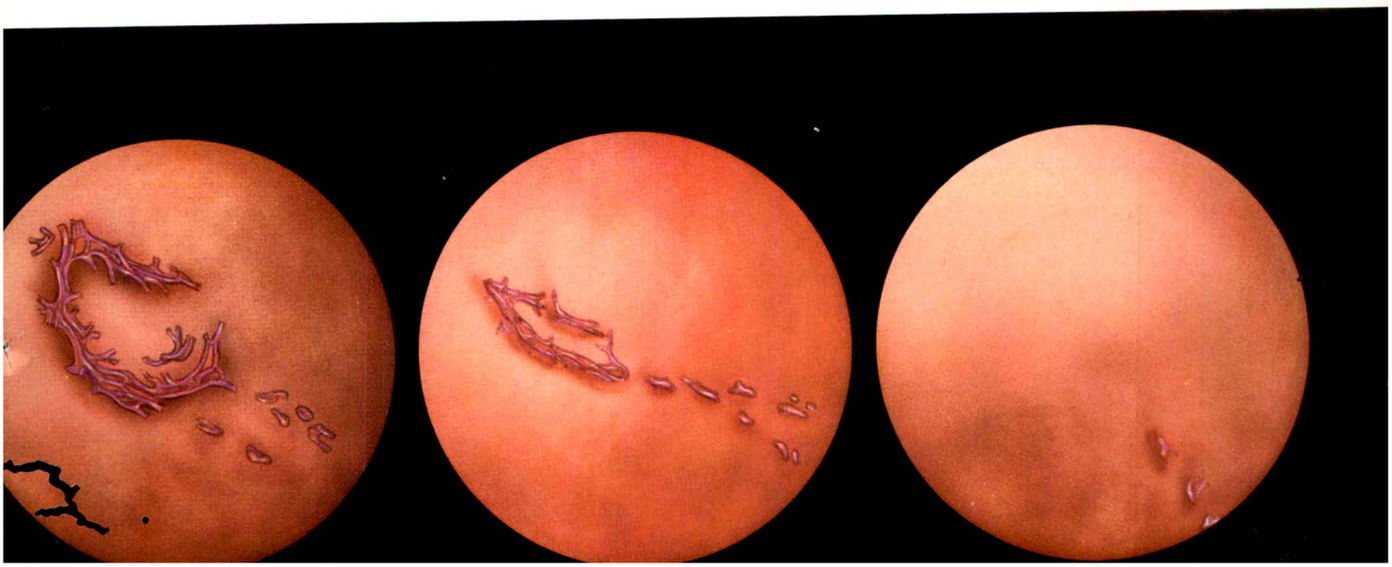
When considering the use of Streptase (streptokinase), comprehensive knowledge of prescribing information and strict observance of the contraindications, warnings, precautions, and dosage and administration instructions are most important to minimize the incidence and severity of adverse reactions, the most significant and frequent being fever, allergy and bleeding. Use of Streptase requires an interdisciplinary effort and therefore should be reserved for those hospitals with facilities for angiography, coagulation testing and volumetric or syringe pump administration of Streptase intravenously.

Hoechst-Roussel has prepared a comprehensive educational program on thrombosis and thrombolysis that includes two films, associated monographs, dosage and administration guidelines and a Speakers Bureau of physicians experienced in the use of thrombolytic therapy.

For information, interested physicians may contact Scientific Services, Room 236, Building M, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876, (201) 685-2611, or the local Hoechst-Roussel Sales Representative.

For a complete list of indications, contraindications, warnings, precautions, adverse reactions and dosage information, please refer to the full prescribing information for Streptase, a summary of which appears on the following page.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876



Streptase®
(streptokinase) I.V.

Brief Summary of the Prescribing Information

Streptase® (streptokinase) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring can be performed. The full prescribing information should be read for complete details.

When considering treatment with Streptase® (streptokinase) the overall clinical status and history of the patient should be carefully assessed. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with Streptase® (streptokinase) therapy than with heparin or oral coumarin compound anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient should be weighed against the potential benefits of treating the patient with Streptase® (streptokinase).

Indications

Pulmonary Embolism: Streptase® (streptokinase) is indicated in adults for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels. It may also be indicated for embolization accompanied by unstable hemodynamics. The diagnosis should be confirmed by objective means. Streptase® (streptokinase) treatment should be instituted as soon as possible after onset of symptoms and no later than five days after onset. Reduction of morbidity or mortality has not been established.

Deep Vein Thrombosis: Streptase® (streptokinase) is indicated for lysis of acute, extensive thrombi of the deep veins in adults. Diagnosis should be confirmed by objective methods.

Streptase® (streptokinase) should be administered as soon as possible after the onset of the thrombotic event (preferably within several days), although slight enhancement of clot lysis has been shown with initiation of therapy up to two weeks after the onset of symptoms.

Contraindications

Predisposition to Bleeding: Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated when the following conditions exist: surgery within 10 days, liver or kidney biopsy within 10 days, intraarterial diagnostic procedure within 10 days, ulcerative wound, recent trauma, visceral carcinoma, parturition (within 10 days), ulcerative colitis or diverticulitis, hypertension, liver or kidney disease, thrombocytopenia or other evidence of defective hemostasis, active tuberculosis, subacute bacterial endocarditis, gastrointestinal bleeding within 6 months.

Predisposition to Allergy: Streptase® (streptokinase) is contraindicated in patients with a history of a previous severe allergic reaction to Streptase® (streptokinase) or who present a significant risk of an allergic response.

Recent Cerebral Embolism, Thrombosis, or Hemorrhage: Treatment with Streptase® (streptokinase) is contraindicated for at least two months.

Predisposition to Systemic Infection: Use of Streptase® (streptokinase) in septic thrombophlebitis may be hazardous because of the risk of inducing systemic infection.

Warnings

Bleeding: Activation of the fibrinolytic system with Streptase® (streptokinase) results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy. Although the aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for lysis of intravascular deposits of fibrin, other fibrin deposits are also destined for lysis and bleeding may result. The possibility of bruising or hematoma formation especially with intramuscular injections is high.

Bleeding at sites of recent invasive procedures may occur. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. Also, invasive venous procedures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observations.

Spontaneous bleeding from internal sites may also occur.

Should serious spontaneous bleeding occur, the infusion of Streptase® (streptokinase) should be terminated immediately.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. These products possess an anticoagulant effect and should be monitored by serial thrombin time determinations.

Predisposition to Cerebral Embolism: Treatment with Streptase® (streptokinase) of patients with conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Allergy: Streptase® (streptokinase) is antigenic, thus, allergic reactions including anaphylaxis may occur.

Recipients of Streptase® (streptokinase) should be observed carefully during the first few hours of therapy. Patients with known allergies to other antigens are more likely to react. If significant changes in blood pressure or asthmatic symptoms occur which might be due to allergy, the infusion should be terminated and symptomatic treatment employed.

Other mild allergic manifestations have also been observed but generally are not serious enough to require discontinuation of therapy.

Use of Anticoagulants: Concurrent use of anticoagulants with Streptase® (streptokinase) is not recommended and may be hazardous. A thrombin time of less than twice the normal control value is adequate for starting Streptase® (streptokinase) infusions safely following the use of heparin. Heparin should not be started following Streptase® (streptokinase) therapy until the thrombin time has returned to less than twice the normal control value.

In order to minimize rethrombosis, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following Streptase® (streptokinase) therapy.

Use in Pregnancy and in Children: Streptase® (streptokinase) therapy during pregnancy and in children is not recommended.

Precautions

If the patient's history gives rise to suspicion of elevated resistance, the streptokinase resistance test should be used to determine the proper loading dose. When resistance levels in excess of 1,000,000 I.U. are found, Streptase® (streptokinase) should not be administered.

Streptase® (streptokinase) infusions have been associated with altered platelet function. Concurrent use of drugs that may potentiate this effect should be avoided.

Adverse Reactions

Incidence and Management

Bleeding: Severe spontaneous bleeding has been documented in 6 of 292 patients during Streptase® (streptokinase) treatment. Several fatalities due to cerebral hemorrhage have occurred during Streptase® (streptokinase) therapy. Less severe spontaneous bleeding has been observed during Streptase® (streptokinase) treatment at approximately twice the frequency as that occurring during heparin therapy. In several instances, spontaneous bleeding has been traced to concomitant anticoagulant treatment which is not recommended.

Management of Severe Bleeding: Streptase® (streptokinase) therapy must be discontinued. If very rapid reversal of the fibrinolytic state is required, treatment with aminocaproic acid (EACA) can be instituted.

Plasma volume expanders are indicated to replace blood volume deficit. If blood loss has been large, Red Blood Cells (Human) may also be indicated. If only Whole Blood (Human) is available, it may also be used.

Allergic Reaction

Incidence: Reactions determined to represent possible anaphylaxis have been observed in 7 of 292 patients treated with Streptase® (streptokinase). These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling, or angioneurotic edema. Other milder allergic effects have been observed in approximately 12% of patients. There was no apparent relationship to dosage.

Management of Allergic Reactions: Mild and moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with corticosteroids administered intravenously as required.

Fever

Incidence: One-third of patients treated with Streptase® (streptokinase) have shown increases in body temperature of 1.5°F or more; the incidence of fever ≥104°F was 3.4%.

Management: Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

Phlebitis: Phlebitis near the site of intravenous infusion of Streptase® (streptokinase) has occurred in less than 2% of patients.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 ml vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows: 100,000 IU (yellow), 250,000 IU (green), 750,000 IU (blue).

In each vial there is a 20% overfill above that stated on the label. Each vial also contains 25 mg cross-linked gelatin polypeptides and 25 mg sodium L-glutamate as stabilizers.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876
REG TM HOECHST AG

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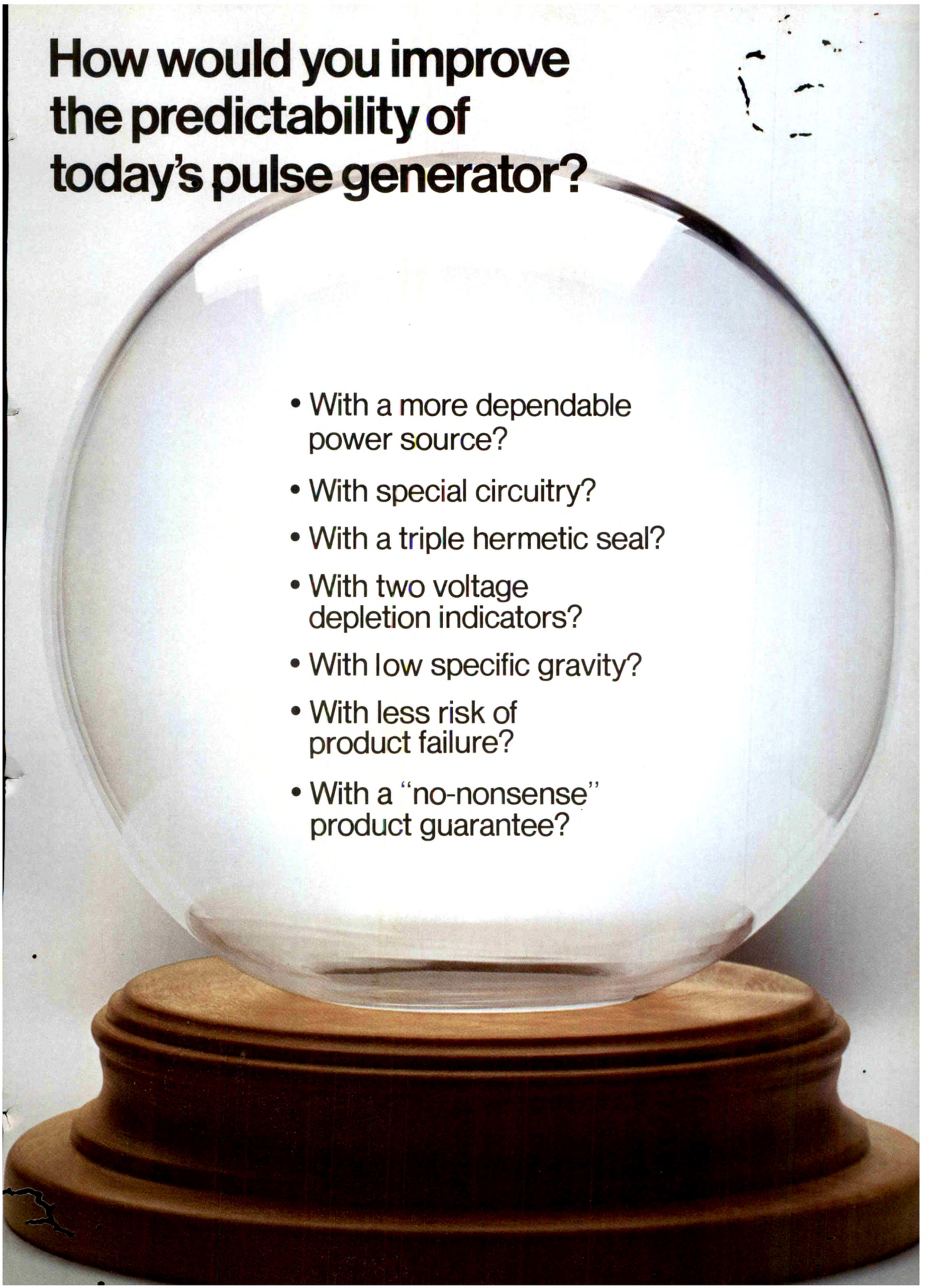
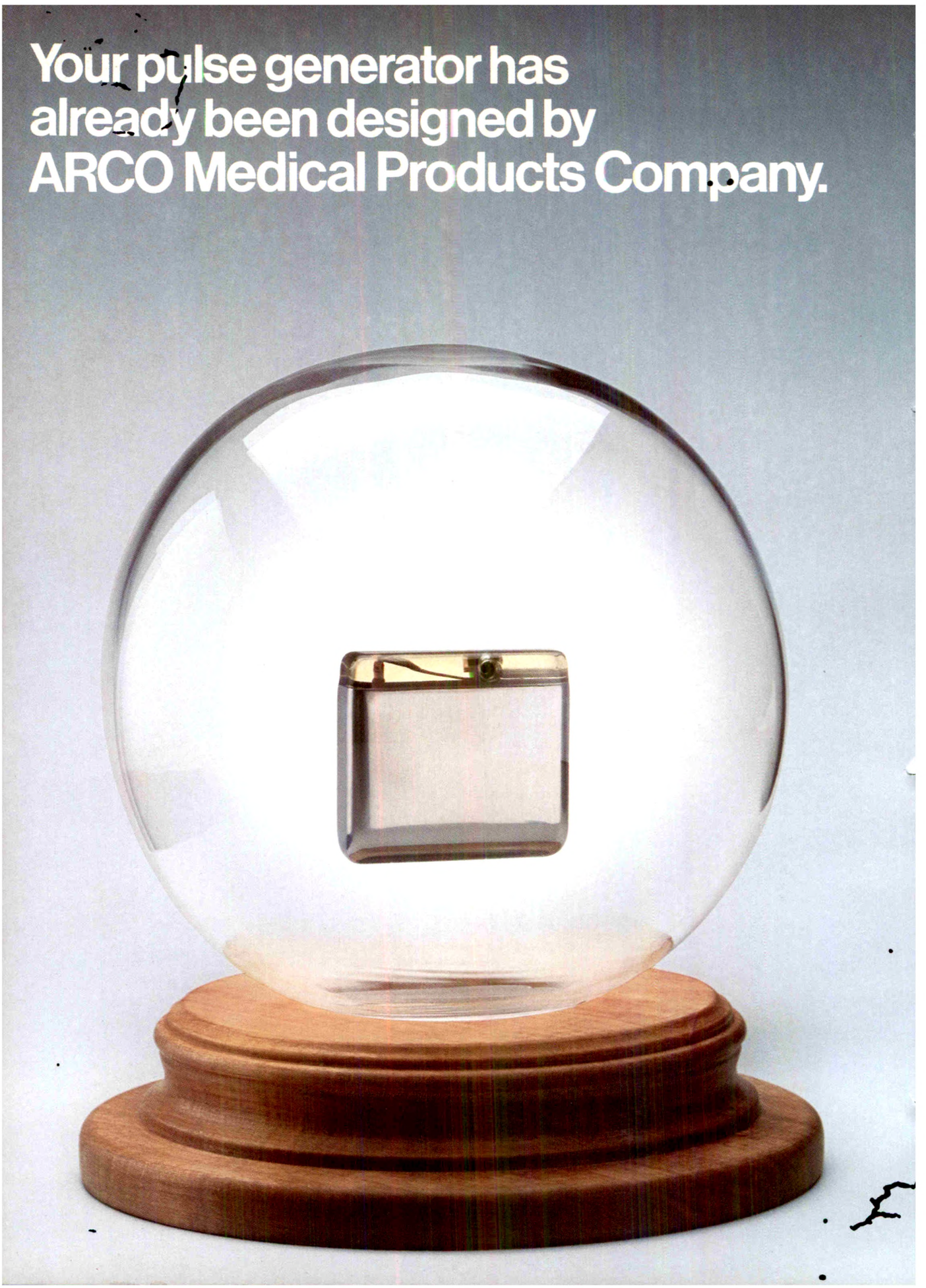
How would you improve the predictability of today's pulse generator?



- With a more dependable power source?
- With special circuitry?
- With a triple hermetic seal?
- With two voltage depletion indicators?
- With low specific gravity?
- With less risk of product failure?
- With a "no-nonsense" product guarantee?

Your pulse generator has already been designed by ARCO Medical Products Company.



Improved predictability with the only lithium thionyl chloride power source.

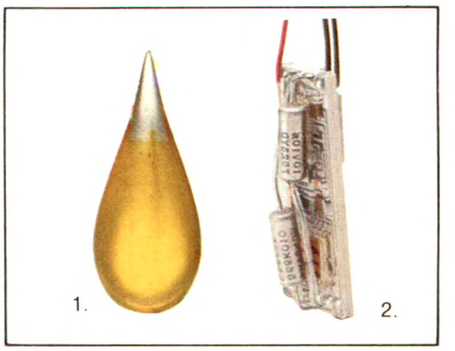
Lithium thionyl chloride, with one of the highest energy densities presently known, permits a small, lightweight battery that is longer lasting than other cells of comparable size in any given application. Individual cell hermetic sealing and no generation of internal pressure contribute to the fact that there has not been a report of a single power source failure in clinical use (1).

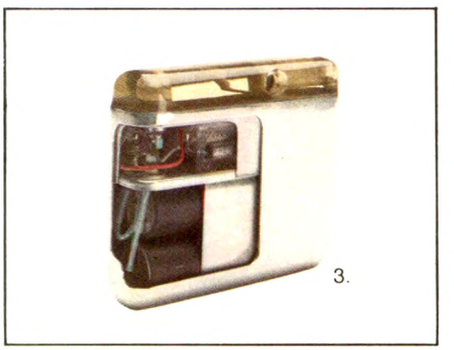
Improved predictability with specially designed circuitry.

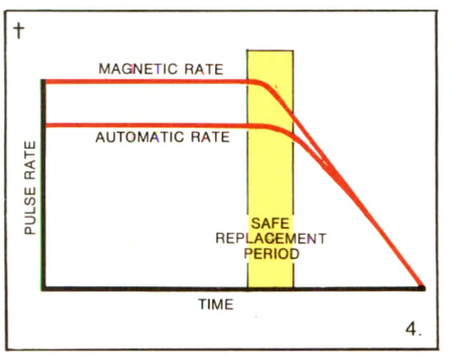
Developed specifically for use with our exclusive power cells, this circuitry offers long life and reliability. In fact, our power cells are electrically connected in a truly redundant fashion, which assures uninterrupted operation even if one cell should fail (2).

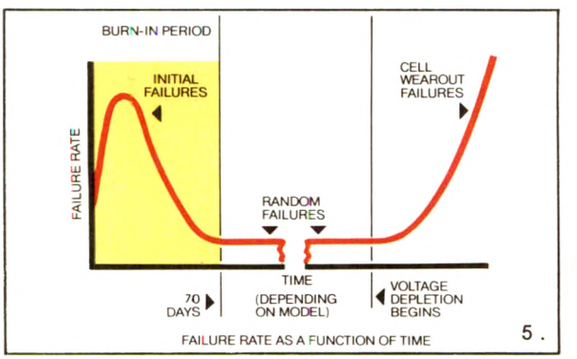
Improved predictability with a triple hermetic sealing process.

The power cells, the electronics, and the outer case of corrosion-resistant titanium are all individually hermetically sealed to provide dual protection and virtually isolate components from the invasion and migration of body fluids (3).









Improved predictability with two voltage depletion indicators.

Both an automatic and magnetic pulse rate provide advance warning of cell voltage depletion. The magnetic rate begins to decrease a number of months prior to the automatic rate to provide ample replacement time (4).

Improved predictability with a more natural specific gravity than most pulse generators.

The specific gravity of ARCOlith™ pulse generators is just slightly greater than that of the body's tissues; thus, migration is minimized for added patient comfort.

Improved predictability with an extended "burn-in" test.

Prior to market release every unit must undergo 70 days of operation. This virtually eliminates initial implant failure and assures you and your patients of effective performance and long life (5).

The predictability of ARCOlith™ pulse generators has been so improved they carry a "no-nonsense" product guarantee.

In essence:

1. Should an ARCOlith pulse generator become defective for any reason up to and including 60 days following implant, we will replace it and pay *all* reasonable surgical and hospital costs.*

2. Should an ARCOlith pulse generator become defective for any reason after 60 days up to the end of the warranty period,* we will replace it and pay up to $200 in surgical and hospital costs.*

*See warranty for specific details. Warranty applies in U.S.A. only.
†Idealized graph based on extrapolated data.

ARCOlith™ 12, 6, and 4 are now the trade names for pulse generator models LI-2, LI-4 and LI-3.

Every ARCOlith™ pulse generator offers you these predictable features:

- Titanium and epoxy casings proven corrosion resistant to body fluids and compatible with human tissue over long periods of time
- EMI shielding, high-reliability filtering components, and special circuits help to protect against electromagnetic interference
- Higher interference rate than the basic pacing rate provides additional protection against PVCs and competition, which may occur at lower levels
- High-input impedance enhances R-wave sensing
- Output stage contains voltage pulse doubler, which allows truly redundant power cells
- Visible temperature indicator informs whether unit has been subjected to excessive temperature prior to implant
- Readily adaptable to most leads
- Captive set screw-in lead connector
- 24-hour telephone diagnostic monitoring of pulse generators available at no extra cost

Disclosure Statement
ARCOlith™ Implantable Pulse Generators

Intended uses: Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to symptomatic bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

Contraindications: There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

Warnings: Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of pulse generators because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

Precautions: The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

Side effects: Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

ARCO/Medical Products Company

Subsidiary of AtlanticRichfieldCompany

Improving the predictability of cardiac pacing

Corporate Headquarters
1500 Market Street
Philadelphia, PA 19101
(215) 557-2000

Technical Center
101 Sherman Avenue
Vandergrift, PA 15690
(412) 568-3663

Operations
P.O. Box 546
Leechburg, PA 15656
(412) 845-8111

Tenth Bethesda Conference

Optimal Electrocardiography*

Cosponsored by the American College of Cardiology
and the Health Resources Administration of the Department of Health, Education, and Welfare
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* The recommendations set forth in this report are those of the Conference participants and do not necessarily reflect the official position of the American College of Cardiology. This study was supported in part by Contract HRA 230-76-0166 from the Health Resources Administration of the Department of Health, Education, and Welfare.

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Optimal Electrocardiography—1977: Introductory Comments

DEAN T. MASON, MD, FACC

In my capacity as president of the American College of Cardiology, I have the pleasure and privilege of opening this Bethesda Conference on Optimal Electrocardiography and of welcoming the present task force participants in the formulation of position papers on standardization, record quality, computers, clinical application, cost effectiveness, and future goals and objectives. My introductory comments will be brief, intended to provide a selected perspective derived from my own view of the subject as a cardiologist.

Modern cardiology now includes a nearly overwhelming array of complex diagnostic procedures of such diversity and sophistication that mastery of all of them is virtually impossible for even the most dedicated specialist. Of these procedures, the first to be introduced and still the most fundamental is electrocardiography. Indeed, until the widespread use of cardiac catheterization over the past two decades, diagnostic cardiology was almost entirely focused upon the electrocardiogram, stethoscope and roentgenogram. A thorough knowledge of conventional electrocardiography remains an essential hallmark of cardiovascular practice. However, it is my general impression that the younger cardiologist today is less proficient in electrocardiographic interpretation than was the case several years ago. This observation is also of concern to the Cardiovascular test committee of The American Board of Internal Medicine, and it is planned that electrocardiographic analysis will be emphasized in future examinations. This deficiency probably reflects a relative overemphasis on more dramatic nonelectrocardiographic techniques in current cardiovascular training programs.

Of substantial importance are the economic costs of electrocardiography to the hospital and consumer, as well as to the clinician. These are difficult to evaluate because of disparities in hospital types and sizes, local situations, financial arrangements, patient charges, equipment and personnel, physician utilization of electrocardiography and other factors in addition to lack of precise data on costs. Nevertheless, with the help of Dr. Zakauddin Vera, director of clinical electrophysiology at our institution, the Sacramento Medical Center University Hospital at the University of California at Davis, we estimated the annual cost of standard 12 lead electrocardiography for all such tracings obtained from inpatients and from outpatient clinics for all hospitals nationally. The 1976 edition of Hospital Statistics lists 1.5 million total U.S. hospital beds with 36.2 million admissions and 254.8 million outpatient visits to all U.S. hospitals in 1975. Prorating these figures to our 400 bed hospital in which we take 25,000 electrocardiograms a year, it is approximated that nearly 84 million hospital electrocardiograms are taken in the U.S. yearly. Assuming noncomputer systems and the hospital expenditure of $3 a tracing at our institution, total U.S. hospital costs for electrocardiograms would be $252 million a year. Thus, total national hospital expenditures for standard 12 lead electrocardiograms appear to account for approximately 0.5 percent of all hospital expenditures (total U.S. hospital expenditures were $48.7 billion in 1975). Another figure of interest is that the Bureau of Medical Statistics of the Department of Health, Education, and Welfare reports that 25 percent of the total U.S. population over 40 years of age has at least one standard electrocardiogram a year. Not included in this analysis of costs and patient utilization are the several additional procedures involving electrocardiography such as vectorcardiography, exercise stress testing, 24 hour ambulatory monitoring, intensive care unit monitoring, pacemaker function assessment and His bundle electrography.

Principal issues requiring resolution and implementation are physician competence and the training and personnel required for interpretation of electrocardiograms. These matters are of particular concern in nonuniversity affiliated hospitals without certified

cardiologists, community hospitals in which the electrocardiography concession may be used as an inducement for hospital admissions and small hospitals that have no internist-cardiologist available. Fortunately, this critical topic is to be thoroughly considered by the members of the present Bethesda Conference and it is anticipated that a core curriculum and an examination in interpretation may be recommended for the purpose of qualification.

Another important subject to be addressed by Conference participants is computer applications in electrocardiography. Computers will be the primary subject of one specific task force, and various aspects of their utilization will be considered by all of the other task forces. My view is that computerized electrocardiographic interpretation has yet to prove itself for routine clinical use. It appears that a person highly interested in these techniques tends to become more of a computer programmer than an electrocardiographer. Computer-aided electrocardiographic analysis may have an important role in certain circumstances, but most investigators emphasize the need for final physician review. Computer systems may approach reasonable accuracy in identifying normal electrocardiograms, but they lack precision in interpretating abnormal configurations, and arrhythmia diagnosis seems to be particularly difficult. Efforts devoted to monitoring programs appear to be more clinically practical at present. However, this is a highly charged topic and there are authorities present who report remarkable success with computerized electrocardiography. The final position paper will be studied with considerable interest.

Finally, I will conclude my remarks on a personal note by paying tribute to the memory of a revered person in my early medical life. This cardiologist, Dr. Robert P. Grant, is well recalled by everyone as the highly effective director of the National Heart Institute in 1965. I remember him most for his kind attention to me in the summer months of the mid-1950's when I was a medical student working at the Institute in Bethesda. He arranged his limited time so that we could meet each day for scheduled teaching periods, during which I was the fortunate recipient of his personal instruction in the concept he introduced of spatial vector electrocardiography. He was a stimulating educator and the first nationally known cardiologist who took a special interest in me. I am deeply grateful for the invaluable experiences with him, and I still have my notebook of those enlightening sessions. Certainly he would be here with us today if it were not for his untimely death.

First the Electrocardiogram—Then What?

A System for Decision-Making by Computer

HOMER R. WARNER, MD, PhD

Electrocardiography has been the proving ground for many of the basic concepts of medical decision-making by computer. This paper describes a system in which these concepts have been generalized for application to the whole field of medical practice.

The HELP system[1] of computerized medical decision-making has been designed to provide the physician with processed information that will assist him in his role as decision-maker. When a system that has access to current medical knowledge in the form of criteria for making deductions and drawing conclusions from observations is coupled to a file containing data on a patient, it can go beyond the task of retrieving and reformatting data. It can help the physician make appropriate diagnostic, prognostic and therapeutic decisions. Decision-making represents the primary role of the physician, and he must bring to this task an ever-growing body of medical knowledge. This rapid increase in new medical knowledge has led to increasing specialization on the one hand and frustration of the generalist on the other. The HELP system is designed to provide consultation based on current medical knowledge to the specialist caring for a patient who has problems outside his special area of expertise and to the generalist who is faced with a problem he may not recognize or a situation in which he lacks experience. Because the system reacts automatically to each new data entry by examining new data in the context of all pertinent previous data on this patient according to rules specified by the medical logic stored in the form of decision criteria, the appropriate medical knowledge will always be promptly brought to bear on each patient's problem. When new knowledge is acquired an additional modification can easily be made to the appropriate component of the system and that new knowledge will automatically be applied to the solution of each patient's problem from that moment on.

Design of HELP System

The basic design considerations of the HELP system and the hypotheses upon which these design features are predicated are shown below.

1. Because experience both in our hospital and elsewhere has shown that it is difficult to entice a physician to enter information into a computer, the HELP system is designed to acquire most of its information about a patient automatically or through paramedical persons. It is designed to make the physician the recipient of information primarily and only in special instances the provider of data.

2. Because the most common type of decision error in medicine is the result of a failure to consider the proper decision, the HELP system is designed to be data-driven. This means that each time a new item of information is added to a patient's file any decisions that make use of that information are automatically processed at that time.

3. Because decision logic is not static over time but changes as new medical knowledge is acquired, logic in the HELP system is stored independently of the computer program that executes it. As new medical knowledge becomes available the decision criteria can be modified without changing any programs in the computer. A common program processes all medical logic and only this common program need be implemented on another computer in order to transfer the medical ware directly.

4. Because the decisions made by the HELP system are to be used in the actual care of patients it is necessary that a physician be responsible for the logic behind each decision. For this reason HELP decisions are expressed in natural language so that a medical expert with no computer experience can generate the logic with enough confidence to assume responsibility for the decisions the computer makes. The decision logic is therefore self-explanatory, which again facilitates transfer of logic developed at one institution to another setting.

5. Because the system is data-driven, the logic for at least one decision is processed almost any time an item of information is entered into any patient's file. It is important, then, that this logic be processed efficiently in order to keep computing costs at a minimum. To accomplish this the natural language source statements representing the medical logic are converted to a tightly coded form ready for efficient processing before they are stored on disc for use by the system. Much effort has gone into this kind of optimization.

6. Because simple approximations to the real logic used by an expert in making subtle decisions will not be accepted in the real world of patient care, the HELP system has been designed to allow the user not only to use sophisticated logical and probabilistic expressions but also to specify complex relations in time sequences among the data required to make a decision. The system, in addition, is hierarchical in order that some decisions may be based on other decisions as well as on raw data to any level desired.

7. Because a very large number of possible decisions might be incorporated in such a system, HELP is designed to be modular so that it can start performing a useful service even with a small subset of its eventual complement of decision logic. This modularity also facilitates division of responsibility for the system logic among experts, each one managing the decisions in his area of expertise. Without this, maintenance of a system with this complexity would become overwhelming.

8. With the rapid advance of medical science, the opinions of experts today may not be considered the best basis for de-

cisions of tomorrow. The HELP system has been designed to provide much of the information needed to improve upon its current decision logic. Thus, there is reason to believe that although decisions made by HELP at the outset are no better than the logic provided by the experts, the system itself can provide data that will form a basis for improved logic in the future.

Source of Data for Decision-Making System

The HELP system incorporating these features has been implemented at the LDS Hospital in Salt Lake City. This is a 550 bed general hospital manned almost exclusively by a staff of 290 specialists in private practice. Of the 150,000 patient records currently in the system, 4,000 are maintained on the active patient disc at all times.

The sources of data for the decision-making system are the following:

1. Each patient on elective admission to the hospital takes a self-administered history while sitting at a terminal.[2] From the answers to these questions HELP decisions are processed on the basis of conditional probabilities to provide the attending physician with a list of suggested diagnoses and the reasons for these suggestions. This procedure and the other components of the screening process are designed to detect secondary problems that may alter patient management because most patients whose physicians use the HELP system are coming into the hospital for elective surgery.

2. *An electrocardiogram* is obtained on each patient during the screening and processed on-line by the computer.[3] The variables extracted by the electrocardiographic program and stored in the patient record are interpreted by the HELP system, both from screening and from signals transmitted from the patient's room over his telephone later in his hospital stay. Comparison of serial electrocardiograms is also made by the HELP system.[4]

3. *Spirometry* is also performed on-line as part of the screening operation. A report of these first three items of information is printed in the screening facility and taken to the ward with the patient.[5]

4. *In the pulmonary function laboratory* several more sophisticated breathing functions, as well as blood gas values, are measured using instruments connected on-line to the computer.[6] Processed data as well as interpretations based on HELP logic are fed back to the technician as part of the quality control process.

5. *In the exercise laboratory* three channels of electrocardiographic information are processed on request from the technician or monitoring cardiologist at various stages of exercise. Signal averaging after rejection of extrasystoles is employed to provide a clean signal for interpretation.[7]

6. *In the cardiovascular laboratory* all hemodynamic data are acquired on-line during the procedure.[8] Left ventricular angiograms are recorded on video disc and then processed by computer to determine left ventricular border coordinates for each frame during a cardiac cycle. A model based on the synchrony of border motion is used to detect areas of abnormal contraction.[9]

7. *The clinical laboratory,* including chemistry, hematology, microbiology and various special procedures, is on-line to a stand-alone laboratory computer system, which in turn interfaces to the HELP system. When these data are verified by each responsible technician, they are transmitted to the HELP system for storage in the patient file. This triggers the processing of any logic that uses that particular data item.

8. *Three files are maintained in the blood bank on each unit of blood*—a donor file, a unit file and a record in the file of the patient who receives the unit of blood.

9. *Every prescription sent to the pharmacy* is entered by the pharmacist through a terminal.[10] The computer prints labels, maintains a drug file for each patient and uses HELP to decide whether that prescription is potentially hazardous to the patient in light of his known sensitivities, other drugs he is taking, his kidney function or other variables that might be deduced from laboratory or other data in his file. If an alarm is generated the clinical pharmacist goes to the ward to bring this information to the attention of the responsible physician or nurse.

10. *Demographic information* obtained during the admitting process may be used for certain decisions.

11. *In the record room* additional information, including the discharge diagnosis, is abstracted from the patient's written chart.

12. *Thirty-one intensive care unit and coronary care unit* beds are monitored directly by the computer for a variety of hemodynamic and rhythm measurements and recordings.[11] Observations by the nurse are entered through the terminal in order to provide a computer record that contains all the information needed for patient care.

13. *Finally, there are terminals on all 31 nursing stations* which are used for entering certain types of information such as increased patient temperatures. However, these terminals are primarily used for reviewing patient data.

Modes of Decision Output to Physician

The decisions made by the HELP system and the data used for these decisions are available to the physician in three modes:

There are four types of routine reports upon which HELP decisions may appear. These include the reports from all of the laboratories, the admissions screening report, the 8 hour shift reports, the cumulative 5 day reports in the intensive and coronary care units and the printed gummed labels attached to the electrocardiograms placed in the chart. A physician may gain access to HELP decisions on his patients through a keyboard TV-type terminal in the doctors' lounge, at each nursing station or in any of the intensive care units. He does this by calling a program that asks him for his code number and then displays a list of patients who are his responsibility. The list of current decisions on any patient may then be examined, as well as the latest data from the sources just described. In addition, from the doctors' lounge or in the intensive care unit, he may obtain a hard copy printout of any of this information.

The third mode of decision output is represented by alerts to the clinical pharmacist in the case of potential adverse drug reactions to a prescription, to a nurse clinician for problems such as an increase in the patient's temperature or laboratory values that indicate several electrolyte disturbances that are not being managed appropriately. In the intensive care unit certain decisions may turn on a red light on the monitoring panel. When a nurse or resident presses that light switch a message describing the alert is displayed on the terminal. Finally, programs are operational that provide the chief of any service with the facility to follow the course of all patients in any category he describes by any logical combination of HELP decisions in the system.

For instance, the chief of pathology is now following up on a day to day basis all patients who have a hypochromic microcytic anemia but who have not undergone a serum iron and iron binding capacity tests.

Illustrative case examples: An example of a HELP sector designed to evaluate the probability that a patient taking the self-administered history has a hiatal hernia as the explanation for his symptoms will serve to illustrate one form decision logic may take in the HELP system (Table I). Items A thru G are variables, each represented by 2 bits in the patient's record. The first bit indicates whether the question was asked and the second whether it was answered "yes." On each question there are delimiters that specify that the last entry of this type of data from 1 month before now until now should be used. Items H thru M specify the parameters of the sequential Bayesean probability estimates to be performed on variables A thru G. The number 14 is the a priori probability expressed as 14 per 1,000 patients in this population being screened who have hiatal hernia. The next two numbers, 570 and 120, in the case of item H represent first the probability of getting a "yes" answer to question A—"Do you have pain made better by milk or antacids?" in patients with hiatal hernia, and the second number, 120, is the expressed frequency per 1,000 "yes" answers to this question given by patients who do not have hiatal hernia. The results of this calculation will become the value for item H and looking at item I item H is then used as the a priori probability in the next stage of the process.

Another type of decision format is shown in Table II. This type not only makes a decision, but also calculates a value that is inserted into the message displayed

TABLE I

A HELP Sector Used by the History Program to Determine the Probability That a Patient Has a Hiatal Hernia Based on His Answers to Each of the Questions Listed

```
SECTOR 3
HIATAL HERNIA (ESOPHAGITIS)
INHIBIT LOGIC = ALWAYS PRINT
*FVAL N
```

```
*A          (A) DO YOU HAVE PAIN MADE BETTER BY MILK OR ANTACIDS. LAST FROM 1 MON BEFORE NOW
*B          (A) DO YOU GET BURNING PAIN IN THE CHEST OR ABDOMEN. LAST FROM 1 MON BEFORE NOW
*C          (A) HAVE YOU HAD CHEST PAIN MADE WORSE BY EATING OR DRINKING. LAST FROM 1 MON BEFORE NOW
*D          (A) DO YOU GET CHEST PAIN MADE WORSE BY LYING FLAT. LAST FROM 1 MON BEFORE NOW
*E          (A) DO YOU HAVE A LUMP IN THE THROAT OR DIFFICULTY SWALLOWING. LAST FROM 1 MON BEFORE NOW
*F          (A) HAVE YOU HAD RECURRING ATTACKS OF THE SAME CHEST PAIN. LAST FROM 1 MON BEFORE NOW
*G          (A) DOES BENDING OR STOOPING BRING ON PAIN OR MAKE IT WORSE. LAST FROM 1 MON BEFORE NOW
*H  PROB  TRIN  A  14  570  120
*I  PROB  TRIN  B  H   680  120
*J  PROB  TRIN  C  I   640   70
*K  PROB  TRIN  D  J   200   50
*L  PROB  TRIN  E  K   400   70
*M  PROB  TRIN  F  L   520  150
*N  PROB  TRIN  G  M   400  140
*O          IF (N LT 14), N = O EXIT
*P          IF (N LT 900) EXIT
```

TABLE II

A HELP Sector That Alerts the Pharmacist If the Drug and Laboratory Values Stored in a Patient's Record Satisfy the Criteria Listed

```
SECTOR 10
PATIENT IS RECEIVING POTASSIUM THERAPY BOTH IV AND ORALLY AMOUNTING TO A TOTAL OF = = MEQ DAILY, SUGGEST
DAILY MONITORING OF SERUM POTASSIUM.
INHIBIT LOGIC = 5
FVAL E
```

```
A.      ELECTROLYTIC, CALORIC, AND WATER BALANCE AGENTS, (A) POTASSIUM REPLACEMENTS, (B) CURRENT, (C) IV, (D) DOSE,
        (E) INTERVAL BETWEEN DOSES (HRS) GET (D*24)/E LAST FROM 2 MON BEFORE NOW TO 24 HR BEFORE NOW
B.      ELECTROLYTIC, CALORIC, AND WATER BALANCE AGENTS, (A) POTASSIUM REPLACEMENTS, (B) CURRENT, (C) IV DRIP, (D)
        DOSE, (E) INTERVAL BETWEEN DOSES (HRS) GET (D*24)/E LAST FROM 2 MON BEFORE NOW TO 24 HR BEFORE NOW
C.      ELECTROLYTIC, CALORIC, AND WATER BALANCE AGENTS, (A) POTASSIUM REPLACEMENTS, (B) CURRENT, (C) ORAL, (D)
        DOSE, (E) INTERVAL BETWEEN DOSES (HRS) GET (D*24)/E LAST FROM 2 MON BEFORE NOW TO 24 HR BEFORE NOW
D. EX   IF (NOT ((A OR B) AND C)) EXIT
E.      A + B + C
F.      IF (E LT 60) EXIT
G.      (A) SMA-6 AND STAT ELECTROLYTES, K+ (X10 MEQ/L) BOOL A NE O LAST FROM 24 HRS BEFORE NOW
H.       EX IF G EXIT
I.      (A) SMA-6 AND STAT ELECTROLYTES, K+ (X10 MEQ/L) BOOL A NE O LAST FROM 48 HRS BEFORE NOW
J. EX   IF (NOT I) STOP
K.      IF (I LT 40) EXIT
```

to the pharmacist. The top message indicates that the patient is receiving potassium therapy both intravenously and orally amounting to a total of____ milliequivalents daily; daily monitoring of serum potassium is suggested. "Inhibit Logic = 5" simply states "Do not print this message if sector 5 is true." (Sector 5 decides if the patient already has hyperkalemia.) Item A prescribes a search of the patient's file for a data field indicating that he is currently receiving potassium replacements intravenously. The GET statement requests the dose (D) multiplied by 24 and divided by (E), the number of hours between doses. This will be the amount of potassium received by the patient in a 24 hour period and will become the value of item A. It will be taken from the *last* field in the time interval specified by 2 months before now and 24 hours before now. Items B and C are identical except for the route, which is, respectively, intravenous drip and oral. Item D is an exit statement that essentially says that if neither A nor B is found in addition to C, do not continue the calculation. Item E calculates the total dose of potassium received by all routes in a 24 hour period. Item F causes the program to exit if the total dose is less than 60 mEq/day. Item G searches for a serum potassium measurement in the last 24 hours and item I for a measurement sometime in the last 48 hours. If potassium has not been measured for 24 hours and the measurement the preceding day showed a value of more than 4 mEq/liter the sector is true, and a message suggesting monitoring for the potassium level will be printed.

STRATO Program

To facilitate the research needed to improve the decision logic of the HELP system a program called STRATO has been developed. With this system a user can create HELP sectors that can then be used to generate subpopulations that fill the criteria of these HELP sectors. For instance, subpopulation 1 might be those patients who had left ventricular angiograms performed before a bypass graft was placed in the anterior descending coronary artery and whose graft was patent 6 months postoperatively while subpopulation 2 filled the same criteria except that the grafts were not functional on follow-up study. A third sector may then be created to define a variable such as that describing left ventricular wall motion in the area supplied by the left anterior descending artery before surgery. The distribution of values for this variable can then be compared in patients from the two populations and the results used to define new decision logic for assisting the physician in choosing patients for this operation in the future.

Clinical Implications

What does the future hold for a system like HELP?

Public pressure is demanding quality assurance and cost control in medicine, and government is responding. The physician dislikes auditing his colleagues. HELP and its counterparts provide a means for providing quality review while corrective measures are still possible for the patient. A system of prompters, probably with a human intermediary such as a nurse-clinician, will prompt the physician when the situation calls for it.

Experience already has shown that such prompting is acceptable only if the evidence for suggesting a particular course of action is convincing. Because much of what we do is based on anecdotes and personal opinion, honest differences exist. Where variations in management plans are not based on scientific evidence, consideration of cost alone may be the appropriate deciding factor.

The ability of HELP to generate data for analysis of medical practice may prove to be its most valuable feature. The accuracy of such data will be enhanced as the decisions made from these data become an integral part of the care of the patients involved. Thus a positive feedback situation is created in which dependence on and utilization of the system by the responsible decision-maker leads to insistence on improved accuracy of data, which in turn facilitates improvement in the analyses done to derive an improved logical criteria for future decisions—and this improvement and verification of decision criteria will influence the physician to place even more confidence in the system.

Indeed, electrocardiographers set a powerful new force in motion when they first used the computer to make interpretations. They should, therefore, assume some of the responsibility for directing the use of this tool into productive channels that will work for the long-range benefit of all patients.

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Electrocardiography and Electrophysiology Are (or Should Be) Friends

HARRY A. FOZZARD, MD, FACC

My purpose is to emphasize that electrocardiography is an application of the well developed scientific discipline of electrophysiology. Because the science of electrophysiology is healthy and growing, we must expect change in our understanding and use of the electrocardiogram. Therefore we must define the latter quantitatively so that it can be kept in step with its science. A second factor that impels me to speak for quantitation in electrocardiography is responsibility to our patients. The electrocardiogram has become such a widespread clinical tool that it has a great potential for good or for harm. We can guarantee its proper use only if we define it.

Origins of the Electrocardiogram

Early in their study of electricity, physicists recognized that it played an important role in biologic events. Not only did electric shocks cause responses in such tissue as muscle, but the muscle itself generated electric currents. During those halcyon days when physicians and physiologists belonged to the same union, the cardiac electrogram was identified by men such as Waller, Burdon-Sanderson and Bayliss. But the great step forward occurred when Einthoven developed a reliable and practical recorder—the string galvonometer. In an obituary for Einthoven, A. V. Hill[1] stated, "Einthoven, *in spite* of his medical training and his office, was essentially a physicist, emphasizing the way in which an aptitude, in Einthoven's case a genius for physical methods, can aid in the solution of physiological problems."

There has been a long and productive exchange between the hard sciences and medicine, with traffic in both directions. I see no reason for it to end. Certainly the development of amplifiers is unlikely to be the pinnacle of scientific contribution to this field.

The Empirical Phase

With the availability of the tool, physicians rapidly began to correlate the electrocardiographic signals with human disease, as in the excellent book by Thomas Lewis.[2] This was a necessary developmental step, but the application of the electrocardiogram soon outran the available understanding of cardiac science. Responsible physicians used the electrocardiogram in spite of the scientific lag, but often found themselves in the realm of science fiction. This empirical use of the electrocardiogram reached its zenith for me when Schaeffer and Haas[3] stated in 1962 that the only justification for the study of the electrocardiogram is its clinical application.

This empirical phase has its giants. I can mention only those I have known personally, and they can stand as examples of the best of this phase. The trio at Michael Reese Hospital—Katz, Langendorf and Pick[4]—have brought a powerful intuition to bear on the electrocardiogram, pointing the way for a generation of electrophysiologists.

Three areas in which electrocardiography has paved the way for physiologic advances are:

1. *Heart muscle as an electrical syncytium.* For years, the evidence for electrical coupling between cells of the heart was obvious from electrocardiographic studies. Only in the last 10 to 15 years have cell physiologists begun to recognize and explore the nature of the gap junction.

2. *Calcium channel* as the basis for excitability in the atrioventricular (A-V) node and other tissues. Although electrocardiographic evidence that the A-V node had a different excitability and conduction mechanism from the rest of heart muscle was overwhelming from the time of Wenckebach and Mobitz, every effort was made to force the A-V node into the "sodium hypothesis." Now we see what should have been obvious, that the inward current system in the A-V node, and perhaps in the sinoatrial (S-A) node, is quite different and depends partly on calcium current.

3. *Accumulation and overdrive suppression.* The influence of a rapid firing rate on subsequent pacemaker rates was clear early in electrocardiography. This has led to the discovery of zones of limited diffusion, near cells, where accumulation and depletion can occur; in this case, accumulation is responsible for overdrive suppression in both the heart and the brain.

Cell Electrophysiology

As the field of electrophysiology recovered from World War II, it prepared for a scientific revolution. With the foundations laid by K. C. Cole,[5] Hodgkin and Huxley showed the ionic basis of the nerve action po-

tential. Armed with the tool of the glass ultramicropipette, cardiac electrophysiologists began to sort out the electrical properties of heart muscle. In spite of warnings from his mentor, Silvio Weidmann began the new era of quantitative cardiac cell electrophysiology with his studies of the Purkinje fiber. After arriving in the United States, Hans Hecht[7] began his work in Utah.

In general, clinicians have contributed little direct effort to this new field. In the "quiet" of laboratories in Brooklyn, Bern, Utica and elsewhere, a scientific foundation for proper understanding of the electrocardiogram has been built, thus contributing greatly to the general field of cell physiology.[8]

Three areas in which cell electrophysiology has contributed to electrocardiography are:

1. *The Hodgkin-Huxley concept.* Hodgkin and Huxley demonstrated the ionic basis of the action potential, with time- and voltage-dependent membrane conductances. These ideas were applied to the heart by Weidmann and many others and demonstrated, for example, the central role of the resting potential in excitability and conduction.

2. *Pacemaker phenomena.* The characteristics of spontaneous discharge have been demonstrated and great progress has been made in understanding of the membrane events responsible for pacemaker activity. The processes involved in pacemaker events have contributed greatly to our interpretation of rhythm disturbances.

3. *Excitation-contraction coupling.* The key role of membrane voltage in turning on or modifying contraction has emerged from studies of potassium contractures and voltage clamps. It is now clear that the action potential shape and firing pattern determine the size of contraction of heart muscle. We are only beginning to recognize the electrocardiographic changes associated with these electric cell events.

Merging of Electrocardiography and Electrophysiology

As the science overtakes the clinical use of the electrocardiogram we will have an exchange between the fields that will be to the benefit of both. *Possible areas of future growth include:*

1. *The role of cell to cell coupling in S-T segment changes and arrhythmias.* We are learning that the gap junctions can rectify. Further, they may change their properties with an increase in cell sodium or calcium or administration of digitalis.

2. *The relation between regional QRS and repolarization currents to contraction.* Knowing that the membrane voltage controls contraction opens up the possibility of electric interactions.

3. *The mechanism of action of a wide range of drugs and hormones.* Day by day our treatment of arrhythmias is becoming more effective and rational through cooperative basic and clinical studies.

The Computer

Nothing is inherently more boring than scanning routine electrocardiograms. I have read perhaps 100,000 tracings, and this number is no doubt small for an active cardiologist. No important case can be made that creative electrocardiographic thinking is directly correlated with simple numbers of tracings read. A machine may assume the bulk of this burden now, but it is fair to ask if it will prevent future progress by cutting us off from our roots. I will argue the opposite. If we use the computer correctly, by defining carefully what it does, it can be a great stimulus to electrocardiographic research. The definition of its task will be to permit growth of our understanding, not to maintain the status quo.

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Present Status of Computer Interpretation of the Electrocardiogram: A 20 Year Overview

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The basic questions regarding health care viewed as a societal issue refer to costs, quality and accessibility. It is difficult to review the whole field. But it is possible to take one small area in which these three questions can be looked at and perhaps answered. Current results tend to suggest that computer electrocardiography can serve as a model for technology's capability in health and medicine and provide insight into use of other technologic aids in medicine. That was, incidentally, the primary goal of my group in the Heart Disease Control Program of the Public Health Service back in the late 1950's,[1–2] when work on computer electrocardiography began.

There has been a 20 year well documented development in computer electrocardiography with relatively complete feedback after a feedforward time period.[3] It is now possible to review the experiences in many centers and to identify whether or how introduction of a technologic innovation has affected cost, quality and accessibility of health care.

To gain insight our analysis must be a medical analysis as well as one in medical economics.[4] It may also have to deal with public policy on health care.[5] The analysis must substantiate whether after 2 decades health planners, developers, scientists, physicians (and perhaps patients) have formed general opinions on computer electrocardiography.[6] We must identify whether we can, from them, define the pertinent questions regarding advantages and disadvantages and reasons for use and nonuse of this tool. From such an analysis we may arrive at a description of the present status of computer electrocardiography and also make recommendations for the future.

Basic Questions

This presentation is confined to an indication of some of the limitations and advantages of computer electrocardiography as I view them looking back over the 20 years since I entered this field. An excellent technical review in this conference by Rautaharju et al.[7] well summarizes other areas. Computer electrocardiography is only a part of this Bethesda Conference on "Optimal Electrocardiography." The real question, as I see it, is how many practitioners recognize computer electrocardiography as an integral part of optimal electrocardiography in the 1970's and beyond?

Electrocardiography is the brainchild of the first systems analyst in the medical field—a physicist turned engineer integrating work previously done in the biologic area with the modern technologic advantages of the communications field, photography and motor drive systems available in the first 5 years of this century. Computers and other newer electronic components have now been added to that technologic complex to allow routine analysis of the wave forms in order to make interpretations. The basic question is whether the introduction of modern technology to the technology of the early 1900's has had a significant impact on patient care.

A recent editorial[8] asked some basic questions, such as whether expenditure of funds on computerization of electrocardiography has reduced inaccuracies in electrocardiograms caused by errors in recording, mounting and reporting. It asked as well whether computerization could aid in validating electrocardiographic results. The first three operational points are easily and quickly answered in a positive manner.

A computer can write or signal significant recording errors to the technician. There is only a minute chance that a computer printout and its electrocardiographic tracing can be mismounted. Additionally, most of the modern commercially available systems have built-in reporting systems that facilitate return of interpretation in seconds to minutes. These attributes, although not clinical, are highly significant to patient care. I am not currently aware of any noncomputer electrocardiographic processing system that can routinely compete with computer electrocardiographic systems in terms of decreasing technician error, mismounting or increasing productivity. At the same time unit costs for these functions with a computer system are lower than those of current manual systems. Yes, more hard data are necessary, but no documented study appears to be available that shows a contrary view. We do not delve too much into those areas when we train students, yet those attributes focus directly on costs, quality and accessibility—today's real medical-societal issues.

The physician must recognize operational attributes as being not less important than the electrocardiographic interpretation itself. In Washington, D. C., as in other areas, third party carriers may pay for the electrocardiographic recording separately from its interpretation. They have properly assessed each component as of identical value. We should not therefore concern ourselves with quality of interpretation as the sole factor for computer electrocardiographic use.

Management and operational attributes have been ignored, in many instances, and systems have not been placed in use because some physicians have looked only at the interpretative side. In such instances physicians may be overlooking part of their responsibility to overall patient care. If half the medical-societal problem is improved, even with the least helpful interpretative program, automation may have overall benefit. It is

necessary to stress a total system concept and to ascribe correct values to each component.

Repeatability of a Computer Answer

The current repeatability (or lack thereof) of diagnosis by the computer using any lead system (or the human being) is much influenced by the fact that in practice the cut-off criteria in electrocardiographic diagnosis are like cliffs. If the R wave amplitude is 1.2 mv, for example, in lead aVL and if we follow certain criteria, we may say that the electrocardiogram is positive for left ventricular hypertrophy. A deep breath in or a deep breath out makes all the difference in the world when such criteria are used. In such instances, a computer analysis, sometimes because of its precision, may not be repeatable, because our textbook criteria have not included considerations of probability (absent as well in all medical school electrocardiographic classes as far as I can determine).

Why is a heart rate of 100 beats/min significant and why is one of 90 beats/min often given little importance? One must consider heart rates, for example, in a population as an increasing slope, and a person's position on that slope has a different probability of abnormality at every level. That is true for any other measurement. We are after accuracy and not precision in medical diagnosis, but our criteria give us only rules for precision—which computers follow better than human beings and are therefore sometimes in error. This suggests that computers need better determination of the ranges we consider "normal." Diagnosticians also need such data. Computers may, as an aside to their basic purpose, help us to obtain what we need.

Computer Analysis in Determination of Standards and "Normal" Ranges

The ultimate purpose of obtaining medical data is to describe the indicators of each stage of disease in a patient so that they can be predictive and lead to prevention of morbidity and mortality in a disease process. Every patient who leaves the hospital with a "healed" myocardial infarction represents a failure or gap in the science of medicine because the infarction was not averted. A basic reason for computer studies is to develop more precise logic so that we can place all possible obstacles in the pathway of disease, even at the earliest stages. This implies that our simple conventional means of separating normal from abnormal is crude. We must obtain numerical values for thresholds all along the course of disease progression. With every change in subject or patient status we should ask the question of where to set "milestone" and "predictive" thresholds.

Toward this end we have been collecting electrocardiographic data from several populations for the last several years, to begin to define various groups by signal data. We have used the electrocardiogram as a model signal. We infer that what we have observed is equally applicable to other medical data.

I can give a summary of impressions. Although we have processed several hundred thousand electrocardiograms, and others have now processed millions, relatively few records have been statistically tabulated, and relevant subclassifications are not available. At present, I can only discuss the general overview of distributions and characteristics of electrocardiographic measurements. However, from the overview of what is still relatively minimal population data we can see that we can begin to gain insight as to what to look for in the specific person.

Electrocardiographic Criteria and Computers

From current computer electrocardiographic data we know that at age 20 to 30 years, 25 percent of persons can be expected to have questionable findings. At age 50 to 60 years, the percentage is about 35; after age 70, it is 51 or more. These observations suggest that the time for a test is not after age 40 or 50 or at the time of a heart attack, but well before age 20, and that repetitive testing is necessary if we are to try to prevent disease.

Consider a group of young teenage boys who have high values for QRS voltage, similar to those meeting the criteria for left ventricular hypertropy. Can we find those boys who do have left ventricular hypertrophy? To determine that a questionable finding exists, a physician generally looks subjectively at levels of measurement. From the conglomerate of those observations, he subsequently determines that there is an atypical, borderline or abnormal situation. The suspicion of abnormality evolves from syndromes of data. When we try to have a computer duplicate physician procedures, we quickly learn that these procedures must be precisely defined. This can be done if we obtain accurate data and clearly tabulate and weight the data that bear on the syndrome.

How can we conclude that a person has a normal heart? If we review data from nonhospitalized ambulatory presumably normal persons and in-hospital populations and tabulate distributions it becomes evident that both hospitalized and nonhospitalized ambulatory subjects have similar value distributions for many measurements. To classify a patient as normal or nonnormal the basic question is, "Is location within the distributions significant as a predictive threshold for disease or possible disease?" In hospitalized groups higher values, such as increased duration of the QRS complex, are clearly related to disease entities. The next question is, "Should the 'normal' population in the portion of the distribution with similar high values be followed up and considered as possibly falling into the same disease categories?"

For another electrocardiographic measurement, the P-R interval, both low and high values in the distribution are associated with abnormality, and the question is, "Where should we set the values for predictive thresholds?" Generally, the P-R interval is considered diagnostic at 0.2 second. This criterion encompasses the upper 5 percent of the population. But are we defining only the classic case and missing the person with a developing trend to the abnormal determination?

Among 25,000 subjects in our studies, 25 percent had Q waves in lead II. Standard practice asks us only to look for a Q wave of a certain width before considering it so we miss what is perhaps an important question, "Is the

very presence of a Q wave of significance and should it have some weight as a predictor of heart disease?" Among the 25 percent that had Q waves it was the hospitalized subjects who tended to have Q waves of greater amplitude.

Should we continue to set cut-off values in our criteria so that only the upper or lower percentile values are used in medical judgments? This seems to be what we now teach medical students. These analyses suggest that varied weighting must be given to each value and each signal. The value of the generally used two dimensional concept of normality and abnormality is limited and will become increasingly limited as computer use continues. Because we are capable of making distinction as to placement within a distribution with computer use, we should do so. We may find that "normality" as distinct from "abnormality" does not exist.

Electrocardiographic Results

A computer system does make mistakes, but any of its results can be validated in an objective manner. Validation of criteria with postmortem findings is often suggested. This is not very practical because most electrocardiograms, for therapeutic use, are taken long before such terminal events. Postmortem study is an ancillary but not necessarily a definitive criterion except in certain circumstances and it should be considered equal in value to an angiogram, a cardiac catheterization or a biochemical determination, all of which should be used for continuing feedback to alter the criteria in computer (and human) programs.

A computer can agree with a criterion set by a panel of cardiologists or one based on cases diagnosed with other means. If computer system error data are contrasted to data on human observer variability it becomes apparent that the computer can help in stabilizing human decisions based on their electrocardiographic interpretations. This is important. Such stabilization can be expected to aid in validating electrocardiographic results.

Computer agreement with a panel of cardiologists (and this really means with textbook criteria, not with the physicians themselves) is perhaps the most usual way of validating results. But past experience shows that once a computer has interpreted an electrocardiogram on the basis of any defined criteria, the computer program designers rapidly receive feedback from those who have other data from other sources. I dare say that data on electrocardiographic criteria and clinical correlation may be far more complete at any large "commercial" electrocardiographic processor's office than in any single academic heart station.

It should be stressed that there is no reason why a computer cannot provide two sets of answers, or more if desired, based on entirely different criteria or lead systems. There is no need for an "either-or" decision, although that is current practice in commercially available programs. I hope that this statement will stimulate that sort of computer output—not to find out which are the better criteria or lead systems but to discover complementary characteristics.

The need for an objective electrocardiographic measurement data pool, as suggested at the onset of computer electrocardiography,[9] still exists. Unfortunately, there has been too much effort and expenditure on studies to determine which program does what best and not enough on studies for constructive changes to the electrocardiographic criteria that physicians use or should use, which could then be easily emulated, and added to, by any or all existing computer electrocardiographic programs.

Computer-Caused Disease?

Some complain because a computer can make a diagnosis (based on real data) that human physicians sometimes omit. In one study with computer electrocardiograms in parallel, physicians based their medical decisions on their electrocardiographic readings and other clinical data, as opposed to the computer's strict follow-up of its preprogrammed electrocardiographic criteria.[10] It became evident that misclassification of subjects was more prevalent among the physician readers of electrocardiograms. Five years later the patients classified by the computer as probably having had cardiac morbidity before the start of the study (and in whom the physicians ignored the computer results) had a statistically significant greater incidence of new episodes of cardiac disease.

The ideas of the 1940's and 1950's about "miseries of heart disease of electrocardiographic origin" are interesting but perhaps should be considered folklore in a day when patients are rapidly and correctly becoming well educated about many of their illnesses. It is necessary, in many clinical instances, to have patients know of aberrations in such detail that they understand the exact meanings of such findings and the problems they may induce. We must explain to patients that there are findings that are atypical and in upper percentile groups electrocardiographically. Patients of the 1970's can well understand the problems of their electrocardiogram if their physician understands and can explain them.

The Problem of Use and Nonuse

The closing paragraph of a Lancet editorial[8] on computer electrocardiography observes that the same mistakes are made over and over again. Unfortunately, the editorial rests its case by suggesting that the European community apparently repeats the mistakes made in the United States by emphasizing efforts to develop standards for evaluating computer programs. The widespread demand for computer electrocardiography has already attracted sufficient suppliers who will adhere strictly (for solid business reasons) to whatever standards are agreed upon for interpretation of tracings *by human beings*. Why evaluate computers first? They will duplicate whatever it is that we wish a human being to do—and then help him to improve that performance!

The clinical limitations of computer-processed electrocardiograms have been studied.[11] Not withstanding these, one can be quite happy that documentation now available shows that the arguments used in 1957 and 1958 to stimulate development of the pioneer system projects were valid. Further, computerization has shown

itself to be a valid answer to clinical as well as medical-societal problems.[4,12]

Recent cost analyses confirm what was postulated from the beginning—for example, that computer electrocardiographic systems can solve some economic problems of concern and thus can be a model for use of other technology in medicine.[12,13] Unfortunately, the government seems to be oblivious of the existence of the model as such, even though it has paid for studies that prove its existence. Recognition of this model for what it is is necessary to maximize its effectiveness. For this reason it is now time for the important bodies that control electrocardiography to recognize the basic user-oriented problems in the field of computer electrocardiography and to implement solutions rather than hedge about the problems.

Can the computer programs solve daily problems in terms of cost, quality and accessibility? The answer, based on the documented literature, is yes. But the utilization of these systems is still small, in contrast to the volume of the ordinary electrocardiogram. We must ask ourselves why growth has been slow and why there has been little acceptance in many medical circles. Three entities stand out, each represented in this room today, as the cause of nonuse. It is time that they were singled out. Industry and many in private sectors have done their part. However, major teaching institutions, government health agencies and professional societies have been waiting in the wings. That should not be their role.

The Academic Institution's Need to Face Grass Roots Problems

A recent request for a proposal from the National Heart, Lung, and Blood Institute is a good example of the problems that must be faced by those concerned with a real-life need to improve quality, decrease costs and increase accessibility of medical care. The proposal is for an electrocardiographic center in a trial secondary prevention program to combat coronary heart disease. One realizes the problems in the use of technology in medicine when a center for advanced research and teaching, such as the National Institutes of Health, considers "one channel ECG recording equipment" "standard" and at the same time considers that "quality control" exists when each electrocardiogram is coded by two coders with "intercoder differences of interpretation . . . adjudicated by the principal investigator or his designate."[14]

Twenty years after computer electrocardiography was considered and developed (outside of the National Institutes of Health), the Institutes still seem stunned by it[15–17] and have moved at a snail's pace into the modern technologic electrocardiographic era. Their sponsored research has therefore been tainted by the fact that their own researchers and those that must bid on their contracts or grants have been deprived or must deprive themselves of higher quality tools and use uneconomic machinery. One could perhaps cite studies that have cost millions and whose results might be adversely influenced by the use of outdated electrocardiographic systems. Yet criticism has been heaped on the pioneer Public Health Service program by academicians at the National Institutes of Health who have not used it and apparently want the world to wait until they develop a better program.[15–17] It is time for parochialism to be brought out into the open, not in a derogatory sense, but to ensure that research institutions understand their role properly.

Until advanced teaching and research centers become intimate with currently available technology it will be impossible, on a broad grass roots scale, to diminish costs, improve quality or make medical care more available. These centers need rapidly to learn about today's cost-reducing technology to be capable of teaching others correct and noncorrect use of technology.

The Need for a Role of Government in Technologic Change

The job of the government is to coordinate, to look at the medical planning aspects of health, to provide guidelines for cost, quality and availability and not, as we increasingly hear from some in government, to complain that practicing physicians are not providing these services. We have seen several government-sponsored studies in the area of computer electrocardiography. They are all good.[4,5,12] However, although almost a decade has gone by, the results and suggestions in those reports have not been implemented. Government officials planning health care are somewhat to blame. One former official in high office, for example, recently wanted to see proof that technology can reduce expenditures for health care but would not spend time discussing even the reports his department funded, much less fund analytical reviews of them to further understanding of potential benefits.

If one uses documented and some government-funded data, one can surmise that there is an average savings in a computerized electrocardiographic system of at least 25 cents a tracing[4,12,13]; the last year has cost our patients some $20 million through noncomputer use. What explanation can health planners in government give for, effectively, the waste of $200 million in the last decade? Is the government really concerned with cost? Is it itself responsible for higher costs by its nonintroduction of cost-reducing technologic measures?

A philosophizing government health planner may tell us that the purchase of electronic equipment is a significant cost. However, $20 million saved in 1 year of computerized electrocardiography could, at present prices, purchase 200 systems for computerized electrocardiography. Modestly, 200 systems, each processing one electrocardiogram a minute (very slow indeed) could process 105 million electrocardiograms a year. We perform only 80 million electrocardiograms a year in the United States. What is wrong with the government economist? The savings in 1 year alone are sufficient to purchase the hardware needed to do the entire nation's job. Yes, coordination would be required to solve problems of implementation and that implies costs, but that's what we already pay the civil servant for. In any event, the basic arithmetic is simple.

The Need for Professional Society Stimulus

The professional society, too, may have ignored some of its responsibility. From the standpoint of the professional society, the views of its members individually or as a group are not in themselves very important. The professional society, because it is not a union, must answer to the public and not to its members. Therefore, the society has to ask itself, "Why aren't we emphasizing the proper utilization of cost-reducing techniques using computers if they can, as the data indicate for computer electrocardiography, improve turn-around time and increase available services (particularly in small hospitals) in the emergency rooms and in rural areas?"

Various professional societies gladly accept exhibit fees from electronics manufacturers, including those that process electrocardiograms by computer, but some associations have been otherwise inactive in this area. The American College of Cardiology sponsored sessions in computer electrocardiography for several years. That was not endorsement but it aroused interest and provided momentum for people to do research and for industry to see what could be done; it also initiated, to a great extent, user trials. I am pleased that the College has again renewed its interest in this model field for use of technology in medicine.

The Professional's Responsibility

Some suggest that cardiologists are expressing their own fears by not using computer electrocardiography. Is there fear that a machine can take over? The question has to be raised whether the answer is positive or negative. I don't particularly care if anyone answers it or not so long as it is brought out into the open.

The new automated radiographic head scanners have not replaced the neurologist; indeed they have increased demands for their services, but at the same time the length and cost of hospitalization for neurologic diagnostic procedures have decreased and the risk to patients from angiography, lumbar puncture and pneumoencephalographic procedures has been reduced. I have not seen the automated blood analyzer displace pathologists—it may even have increased their income; at the same time, unit costs have decreased for their patients and accessibility to more precise tests has increased.

Were the automated blood chemistry analyzers always as good as they are now? Have there not been serious errors in early versions of every medical product—capably circumvented by the wise user thereof? Why is the cardiologist afraid? Is it concern about income? Is it fear of displacement? Is it really considerations of quality?

Conclusion

The basic documentation is in. We should not, I believe, do more studies. We should not wait another 20 years and lose the $20 million a year in patient savings with computerized electrocardiography, lose 60 percent of cardiologists' time spent in reading electrocardiograms[18] or lose half of the time of the clerical services in the heart station, and continue to have inconsistent, unstandardized answers with the observer variability that is common to all of us.[19] A logician once said it was worthwhile pointing out faults if they are correctable. I have highlighted in my overview what I think are faults, but I do so only because of faith that the academic institution, the government, the professional society and the cardiologist will correct the existing faults for the benefit of the patient.

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The Quest for Optimal Electrocardiography

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For in the study of nature the human mind may really approximate that god-like objectivity which it fondly, but erroneously, imagines itself to possess when it studies the facts of human history. In the field of history it is no pure mind which observes the facts, but an anxious reason, organically related to an anxious ego, reacting with pity or scorn, with fear or pride, to the greatness or the weakness, to the promised support or the threatened peril, of this or that competitive expression of human vitality.

—Niebuhr[1]

There is a distinct hazard that, in attempting to interpret history, we will discover only the fruits of the biases we brought initially to such study. Nevertheless, we need to look at the past both to understand the present and to plan for the future. Mindful equally of the hazard and of the need, let us look briefly at the history of electrocardiography and then examine three topics related to the quest of this Bethesda Conference: the nature of electrocardiography, the ingredient of human engagement in human enterprise and the identification of the optimum or the best.

Nature of Electrocardiography As Seen in Its Development

To determine the scientific basis for a clinical practice is a relatively straightforward undertaking, but to trace the scientific origins of any clinical advance is a nearly impossible task. Recently, however, Comroe and Dripps[2] published a careful and scholarly examination of the scientific history of 10 major advances in cardiovascular and pulmonary medicine since the 1940's. They found that 137 different scientific fields formed the necessary background and that more than 2,500 significant events or publications contributed to the development of these fields. More than 500 articles (1 of 5) were called key in that they were essential to subsequent development and eventual clinical application. I have derived Figure 1 from their tabulation of the events and publications in the development of electrocardiography. The labeled steps correspond to Comroe and Dripps' assessment that they were key to subsequent clinical advance.

The background leading to electrocardiography has passed through successive but overlapping phases: the era of electricity, the era of bioelectricity (differentiating into cardiac electricity) and the era of cardiac electrical sequence. First, electricity in nature had to be identified, and an instrumental means of reproducing it on demand had to be devised. Next came the successive concepts of electrically active tissues, the relation of muscle contraction to electrical discharge, cardiac action currents and the systolic refractory period. Then, as the actual recording of the electrocardiogram in animals and man passed through instrumental refinement, there simultaneously proceeded the serial discovery of anatomically distinct cardiac tissues: Purkinje fibers, atrioventricular bundle, atrioventricular node and sinoatrial node. The recording apparatus and the anatomic-physiologic identifications were necessary to begin the study of the excitation and recovery sequences. Study of the normal sequences began to lead to expectations for surface electrocardiographic wave forms. These expectations became generalizable in the vector concept of Wilson and, from these expectations, diagnostic clues concerning orientation, chamber size, myocardial gain (hypertrophy), myocardial loss (infarction) and altered recovery emerged. From the study of abnormal sequences the foundations of arrhythmia analysis were laid. And as each successive layer of knowledge accumulated and the more exquisite detail of recording and interpretation appeared, our understanding of cardiac electrical activity grew and became more complex.[3–6]

Three messages may be derived from consideration of the data in the diagram in Figure 1: (1) The worth and development of each discovery depends upon preceding and succeeding contributions of others. To the events not labeled is attached an impressive catalog of illustrious names. (2) Only initiating or trigger articles from an extensive volume of published work are indicated; many significant contributions that have fleshed out the body of knowledge of electrocardiography are not even listed. (3) Because of the pragmatic criterion of eventual clinical application, the steps from 1925 onward may soon come under dispute. In this transient view, instruments such as the cathode-ray oscilloscope, the silicon diode and the digital computer are convenient but not yet established as clinically necessary. Similar exquisite knowledge of ion currents in electrically active cells and of cardiac potential distribution over the body is interesting but not yet empirically useful. At any rate the list will be appreciably augmented when reviewed and reassessed in the year 2000 in the light of the then manifest clinical advances in cardiovascular and pulmonary medicine.

Finally, the diagram and the discussion have hinted at the nature of the field called electrocardiography. It is a process rather than a product. This distinction can save us from much anguish whether we consider the field either in its illuminative aspects or in the derivative narrower view of pragmatic diagnostic applicability. Neither diagnostic nor investigative electrocardiogra-

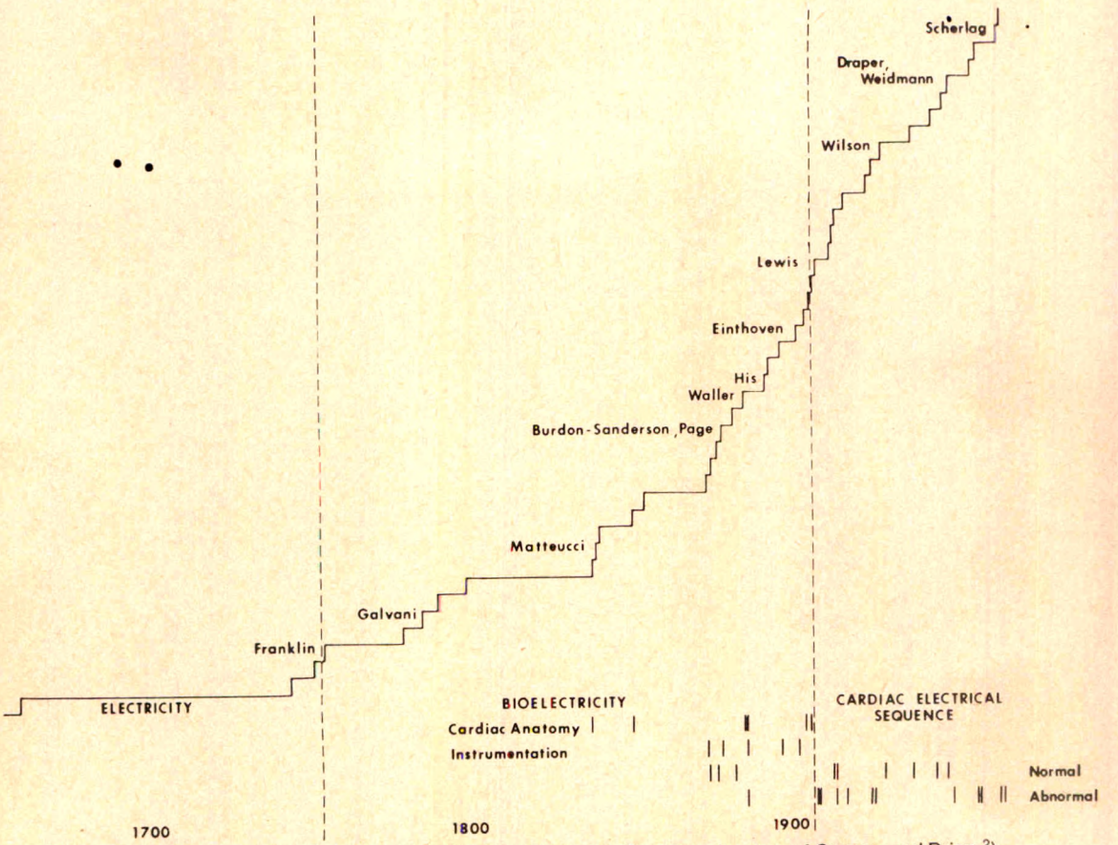

FIGURE 1. Steps in the development of electrocardiography. (Based on the data of Comroe and Dripp.[2])

phy is a product; both are processes. What is the product of each? I think the answer is not—and should not be—neatly forthcoming. For some, the product of diagnostic electrocardiography is an array of scalar wave forms clearly mounted and displayed; for others, the measurements and verbalization describing those wave forms; for still others, both. Further variations as to what actually constitutes the product may include interpretive remarks concerning recognized or suggested categories of abnormality or statements about the probability of their association. Scalar display, description and categorization may be extended to vectorcardiographic counterparts.

The current products of investigative electrocardiography are quite varied in form: His bundle electrograms, body surface potential maps, membrane action potentials—all displayed, described and interpreted in contexts related to their locale and purposes of origin. The great variety of these approaches is significant because each in its individual format yields data rapidly becoming valuable to the clinical electrocardiographer.

Human Engagement in Human Endeavor

Let us turn aside momentarily to examine in analogy the relation between purpose and means in three fields of human enterprise: warfare, biology and medicine. The parallels run in this fashion: The practice of war is a subspecialty of politics and has to do with whether or not one group of men does or does not impose its will upon another group. In war the offensive purpose is to be able to cause the other group to do what we want them to do; the defensive purpose is to prevent the enemy from being able to dictate the manner of daily life to our group. The methodology or strategy requires that the practitioner engage the enemy in battle and destroy his warmaking capacity. Note the phrase "engage the enemy." Bruce Catton[7] points out that the Union cause did not proceed militarily until Lincoln placed in command a general who understood the basic premise of engagement. Let us borrow the term engagement and use it to mean thorough, skillful, wary, energetic and "hands-on" involvement.

By analogy, the practice of biology is an inquiry into the processes of life, and the practice of medicine is the diminution of illness and its sequels. The strategy in biology requires the practitioner to encounter the various life processes wherever they may be found but then to engage them on terrain wherein he can observe them, test them and perhaps even understand or predict them. The strategy in medicine requires that the practitioner encounter the problems and phenomena of human illness and arrange to engage them under conditions where they may be comprehended and altered, attenuated or accepted.

There is a need in any worthwhile human endeavor for substantive engagement. In biology the engagement is with the processes of life; in medicine, with the problems of the sick. In electrocardiography, it is with electrical outpourings of the heart. We have talked thus far largely about the object of engagement rather than the subject. In war if we are to engage the enemy, someone must be trained to do it. The group that depends completely on storing all the information from the last war in libraries, computers or arteriosclerotic generals has made either a vastly incomplete or a vastly unnecessary investment.

In brief, for these three endeavors (war, biology and medicine) the respective purposes are to win (that is, enslave or be free according to viewpoint), to understand or to heal. For each the means are twofold: to engage (the enemy, the processes of life, the problems of illness, respectively) and to apply available knowledge, experience and technical skills—either intrinsic to the endeavor or borrowed from other fields—in order to master the object of the engagement.

From the purposes and strategies of the two major fields of biology and medicine, electrocardiography must draw its value system; from our interpretation of the term optimum we may decide whether the study of the electrical activity of the heart is to be viewed more as a means or as an end. Armed with these brief considerations let us examine the concept of the best.

Identification of the Optimum

Optimum (or optimal) has two basic meanings. The first is that which is most conducive to a given end; the second is that which is the best result under the given circumstances. Thus optimal electrocardiography may describe either the best *means* or the best *result*. This immediately raises the question of whether we consider electrocardiography a means or an end. If a means, a means to what: Is the role of electrocardiography exclusively that of an agent of clinical inquiry? If so, what is the form most likely to lead to the maximal sensitivity, specificity, utility and economy of presentation of evidence? On the other hand, is the art of electrocardiography an end unto itself? Is the study of the electrical activity of the heart complete? Or is it worthy of still more attention and contribution from physicians, physiologists, physicists and engineers? If so, what forms are likely to lead to the deepest insights?

There is an old folktale about the key flower. When a wanderer found and plucked the flower, the hillside opened revealing the entrance to a cave. Inside sat a kobold who welcomed the visitor, "Come in; take all you want, but don't forget the best." With a wave of his hand the elf indicated a vast storehouse of riches: gold, silver, precious gems and lovely works of art. The visitor stuffed his pockets, his sleeves, his socks, his hat; adorned himself with rings, bracelets, necklaces. But each time he started to leave, the elf repeated the injunction "Take all you want but don't forget the best." So the man would rush deeper into the cave exchanging what he carried for something that seemed finer or more precious until at last he felt his survey complete and staggered out. The hillside closed and he began to examine his finds. But his pockets contained dull rocks, dry leaves and the fortune withered before his eyes. He was indignant and turned back. There was no seam in the hillside and no clue of a way back into the cave. He then remembered the flower—that magnificently beautiful but simple key to the hidden store. But it lay prematurely forgotten and now irretrievable somewhere on the floor of the cave.

Examine now with me a random sampling of the many goods that come from or that may arise from electrocardiography. Then let us imitate the wanderer in the legend and nominate which of all these goods is the best of electrocardiography and most worthy of presentation.

1. *Diagnostic signs:* Electrocardiography contains a treasure of well recognized diagnostic clues to structural and functional abnormalities: atrial and ventricular enlargement, myocardial infarction-injury-ischemia, acute electrolyte imbalance, cardioactive drug effect, acute intracranial injury, cardiac conduction defects, simple cardiac arrhythmias.

2. *Monitoring capacity:* The electrocardiogram provides a convenient monitoring device in a variety of states. These range from heart rate and rhythm and S-T segment monitoring during sample days of the patient with unexplained syncope to similar but tethered monitoring of the resting patient in the cornary care unit with a suspected ischemic event or to the exercising patient with suspected limitation of perfusion.

3. *Arrhythmia analysis:* In addition to these two large groups of readily codifiable abnormalities or criteria, the body of electrocardiographic understanding has come to include a distinctive field of arrhythmia analysis. Such analysis cultivates detective-like skills in the clinical observer, causes him to examine the cycle length-coupling interval relation, to search for "motive" and opportunity and to construct and validate from such search clinically appropriate hypotheses as to the immediate problem in impulse formation and conduction.[3] This approach is uniquely human, and not likely to be easily, economically or appropriately imitated by computer programming.

4. *Direct physical evidence in the physician's hands:* Clearly allied to the billions of observations made by human observers that led to codifiable signs and criteria and the hundreds of thousands of analyses that led to the variations on the ladder diagram is a distinctive—almost unique—property of the electrocardiogram on the clinical chart: it is a form of nonverbal communication from the patient's heart to the physician. When properly and systematically recorded it permits the doctor to relate wave form and time relations to the other characteristics of the particular patient. The words and fashions of an impersonal reader may sometimes be contributory but the presence of the raw data provides direct communication and an unblinded reference for future comparison.

The role of the continuing student of electrocardiography in practice has still another aspect. Anyone acquainted with current medical practice is familiar

with the two-edged nature of the laboratory procedure that has left the immediate control and direct examination of the appropriate clinician. On the positive side of the ledger are the advantages of such a transfer: (a) economy from centralization and mass production, (b) the increased likelihood of standarization by increased concentration or volume of production, (c) disinterested interpretation and certification, and (d) the possibility of greater technical quality control by a supervisor not beset by competing clinical, investigative or administrative responsibilities or interests. On the negative side of the ledger are the disadvantages: (a) the previous economy may be offset by the expense of overcoming the problems of misrouting, delay and loss in an extensive communicative network, (b) the psychology of standardization proves a serious obstacle to necessary change in technique as the state of knowledge changes, and (c) the supervisor who is interested only in the statistics and economy of mass production not only resists change but fails to make the key observations from which innovation springs and, even worse, fails to bring previous and current knowledge to bear in interpretation.

5. *The continuing engagement of human intelligence:* Regardless of the acknowledged difficulties with lack of uniformity in readers, the great number of physicians with direct access to and deep interest in the raw material of the electrocardiogram has produced a continuously evolving body of knowledge. I would nominate as one of the great goods of electrocardiography the breadth and intensity of interest that has caused such a flow of information between the basic scientist and clinician. The electrocardiographic clues to electrolyte shifts have predicted ion currents whose study in turn has led to deeper perception of electrocardiographic morphology. The ping-pong from the clinically evolved concept of concealed conduction to the laboratory-evolved concept of the dual A-V nodal pathway to its clinical recognition began a productive interchange that continues to reciprocate between clinic and laboratory. Indeed, the His bundle electrogram daily reminds us of the dynamic fusion between clinical and laboratory observation, characteristic of the history of electrocardiography.

I believe that electrocardiography serves two inextricably linked purposes: the understanding of the biologic processes of the heart and diagnostic perception of problems in cardiac structure and function. I believe that in the service of these purposes, from the tradition of Waller, Einthoven, Lewis, Wilson and a succession of giants, we have evolved a large and sophisticated cadre of electrocardiographers: dedicated life-long students of the heart, skilled observers, skilled analysts and patient discoverers. I believe that whatever we do further to standardize, codify or reduce to programmatic form that portion of the body of electrocardiography susceptible to such management, we must take extraordinary pains to preserve the stimulus and opportunity that keeps that cadre fit. We may program computers to read electrocardiograms; we must not deprogram doctors. We must continue to learn and to teach electrocardiography as it continues to evolve so that tomorrow's physicians and scientists will be equipped to share tomorrow's knowledge for the solution of tomorrow's problems. It is critical for us as custodians of the resources that we must eventually bequeath to those who follow that we carefully make no choice that purchases transient economy by the creation of massive ignorance.

Otherwise we will have forgotten the best.

Acknowledgment

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Task Force I: Standardization of Terminology and Interpretation

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The development of a soundly based, widely acceptable uniform terminology for electrocardiographic interpretation is difficult. Physicians frequently disagree about the classification of features in an individual record, and similar disagreements occur in reports generated by different computer programs.[1–10] Some disagreement results from technical error, but the remainder arises from differences in measurement technique, terminology and criteria. Standard rules for measurement, classification and description of electrocardiographic features appear desirable to improve patient care by improving the consistency and quality of the report as well as communication between the interpreter and the user. The standards should be flexible enough to provide for continuing incorporation of improvements in electrocardiographic diagnoses, for classification of features from different populations and for different categories of users.

Standards for medical procedures are more readily accepted if they are logical, easily understandable and authoritative.[11] However, significant variability in electrocardiographic classification persists even when physicians agree to use identical criteria.[4–6] Imprecise identification of the onset and offset of electrocardiographic deflections is one source of variability in classification procedure, but this type of error can be minimized by proper selection of criteria.[12,13]

There is no comprehensive list of definitions and criteria designed for the use of electrocardiographic interpreters. The New York Heart Association monograph on nomenclature[14] focuses on comprehensive cardiac diagnosis rather than the electrocardiographic report. One of the best known digital coding systems, the Minnesota Code, has precisely defined criteria for classifying electrocardiographic features but is more useful in large scale clinical studies than in the interpretation of routine clinical reports.[15,16]

Types of interpretive statements: Selecting criteria for each electrocardiographic interpretive statement may be more difficult than selecting terminology. Statements can be divided arbitrarily into three types: (1) Type A refers to an anatomic lesion or pathophysiologic state that can be verified by nonelectrocardiographic evidence; this includes hypertrophy, infarction, ischemia, pulmonary disease and drug and metabolic effects. Selection of optimal criteria for type A statements depends on confirmatory nonelectrocardiographic information, which is limited in many instances at present. (2) Type B refers to an anatomic or functional disturbance that is detectable by the electrocardiogram itself (including special intracardiac leads). Criteria for these statements are based on characteristic features, and pertain mostly to arrhythmias and conduction disturbances. (3) Type C refers to electrocardiographic features that do not fit into type A and B categories. These include electrical axis, nonspecific T wave abnormalities, "premature repolarization," and unusual voltage. It appears reasonable to define interim standards for types B and C statements at this time, with the understanding that they may be modified by additional information.

Selection of criteria: For any type of electrocardiographic statement criteria should be selected with regard to sources of uncertainty that determine the accuracy of the statement; this principle is common to all medical diagnoses.[11,17–21] With respect to electrocardiographic diagnosis, numerous sources of uncertainty include physiologic variations from complex to complex or from day to day, variations in recording equipment or technique, recognition and measurement of the recorded wave forms, morphologic and etiologic classification of electrocardiographic features, and inadequate communication between the interpreter and user of the report.[2,22,23] Criteria for classification into different categories should not depend on a difference between measurements resulting from chance variations.[2,24] Borderline regions should be defined on the basis of total precision for both the measurement and the criteria.

The definition of pathologic states responsible for the electrocardiographic changes is not necessarily precise. This may complicate establishment of valid criteria. The problem of classifying "microinfarcts" in a correlative study of electrocardiographic criteria is one example of this situation.[25]

Variations in electrocardiographic measurements associated with age and other constitutional factors make it imperative that all comparisons be made between similar population samples. Collection of data from large samples of healthy and diseased populations

will be helpful in estimating the performance of various criteria. The same principles can be applied for data from multivariate statistical analyses or from recordings with special leads.[26–28] Comparison among electrocardiographic criteria should be based on sensitivity and specificity for a series of limits rather than for a single point. Plots of this information provide sensitivity-specificity curves that demonstrate relative performance of different criteria for various circumstances.[11,17–20,26] (Similar curves have been described as "receiver operating characteristic" or "diagnostic operating curves."[11–17]) A particular level of sensitivity or specificity can be selected from such curves for a given purpose.

Terminology: Preferred terms should be selected according to their scientific accuracy, understandability, simplicity and current use, in that order of priority. A critical evaluation should be made of supporting logic and data before selecting any new or uncommonly used term. A recent study of arrhythmia nomenclature illustrates the importance of this approach.[29] Care must be taken not to discard commonly used terms to gain a small or hypothetical improvement in scientific accuracy at the expense of a significant loss in understandability. Abbreviations, acronyms, slang, parochial terms, rare eponyms, jargon and complex terms should be avoided. Terms should be selected and grouped in a consistent manner. Exceptions to these guidelines may be desirable if they improve understandability.

Definitions for the selected terms should be provided; statistical and other information on which these criteria are based should be described and reasons given for the choice when commonly used alternative criteria are available. A concise set of instructions for use of these terms should be provided along with a list of modifiers to indicate such items as probability, location and age of lesions. These are discussed later.

General Classification Terms

Two different meanings for *normal* are currently used in medical practice. One is based on prevalence and the other on health. When the meaning based on prevalence is used, *normal* is defined in Dorland's Illustrated Medical Dictionary and Stedman's Medical Dictionary as "typical," and "agreeing with the established type," and abnormal is defined as "contrary to the usual. . . ." However, when the meaning based on state of health is used, *normal* is defined as "healthy" and abnormal as "not healthy."

There are limitations to the usefulness of each of these meanings. Some physicians have a preference for one of the two, and others use both. A serious error can result from a misunderstanding as to which meaning is being used in a specific situation. The different preferences of physicians make it unlikely that unanimity could be achieved by an appeal for standard terminology. A recent suggestion that the term *normal* be discarded and replaced by more meaningful synonyms seems unrealistic for the same reason.[30] A different approach consists of requiring that *both* prevalence and health conditions be satisfied when either the term *normal* or *abnormal* is used. Electrocardiographic features that are not usual for a healthy population and not commonly associated with disease would be classified as *atypical* rather than as abnormal. This should lessen conflict and misunderstanding in use of the terms.

Definitions

Healthy population: Persons constituting a category without disease.

Healthy population sample: A representative sample of ambulatory noninstitutionalized persons without medical complaints or evidence by history or examination of any disease or dysfunction that may impair health or affect the electrocardiogram. The sample should be stratified by age, sex, race and body build characteristics. Healthy persons with other special characteristics that may affect the electrocardiogram (such as unusual physical activity or altitude acclimatization) should be considered separately. The logic and methods for selecting and stratifying a healthy population sample have been described and used by Simonson.[2]

Normal: An electrocardiographic feature that is within a specified normal range limit for a sufficiently large and appropriately stratified healthy population sample. It is preferable to establish the normal limit from a percentile distribution rather than from the standard deviation or the extreme range for the distribution.[2,30–32] The standard deviation is less preferred because some important electrocardiographic features do not have symmetrical (Gaussian) distribution.

The most complete source of electrocardiographic information analyzed in this manner is in the monograph by Simonson.[2] This information is suitable to define normal limits for current use, but it would be desirable to record and analyze a larger sample from healthy persons, using multichannel recorders and computer techniques, and perhaps establish other percentile distributions (such as 1 and 99, 5 and 95, and 10 and 90) for both individual and selected groups of electrocardiographic features.

Abnormal: An electrocardiographic feature that is outside a normal limit and has a significantly greater prevalence in diseased than in otherwise similar healthy persons. Correct classification of an abnormal feature presents difficulties when the measurement overlaps between the distribution curves for healthy and diseased populations. In such cases probability of correct diagnosis depends on the proportion of healthy and diseased persons in the total sample of interest.

Atypical: An electrocardiographic feature that is outside a normal limit and does not have a significantly greater prevalence in diseased than in otherwise similar healthy persons.

Borderline: This term is a modifier for normal and abnormal. It denotes uncertainty as to the particular side of a criterion demarcation line a finding belongs on. The accuracy and variability of an electrocardiographic measurement, the location of a criterion demarcation line or a combination of these factors may be the source of the uncertainty. The borderline zone may encompass only a few milliseconds or microvolts for a measurement that has a high degree of precision and accuracy but may be considerably wider if the degree of precision or accuracy is low.

Borderline normal: An atypical electrocardiographic feature that is outside a normal limit by less than the sum of chance error for determination of both the limit and the individual measurement. Simonson[2] suggested that *borderline* be defined as a measurement that exceeds the percentile limit by less than four times the standard error for the limit plus the standard deviation for the measurement.

Borderline abnormal: An electrocardiographic measurement that is closer to a criterion for abnormality than 1 standard deviation for the measurement error.

Normal variant: This descriptive term may be used for an atypical electrocardiographic feature or one that exceeds a criterion for abnormality in a person known not to have the disease suggested by the criterion.

Classification of the total electrocardiogram: The classification of a clearly normal or abnormal record is simpler than classification of one that contains atypical or borderline but no definitely abnormal features. It has been suggested that at least one atypical or borderline measurement will be present in any electrocardiogram from a healthy person as a result of chance because of the large number of measurable variables. Furthermore, it appears likely that multivariate analysis would reveal an association between some groups of atypical or borderline features and disease.[27,28] In the face of insufficient information, we recommend a conservative statement such as "Electrocardiogram contains borderline findings, otherwise normal."

Choice of terms: Some terms refer to a specific anatomic or physiologic state; others are simply a description of an electrocardiographic feature with an option for suggesting one or more possible causes.

Preferred terms: Selection of preferred terms is based on factors mentioned earlier in this report. Alternative terms are mentioned if they are in common usage or are considered equivalent to the preferred ones.

Modifiers: These are used to indicate an estimated probability that a statement is correct, an anatomic location or age of a lesion or the frequency of an intermittent feature.

Age: Terms relative to age are used most frequently as modifiers for statements on myocardial infarction. The phrase "age undetermined" may be followed by a probability modifier and one of the other age terms; for example, "age undetermined, possibly recent" or "age undetermined, probably old." The terms "acute" and "recent" may be used with statements that relate to a pathophysiologic condition, such as *myocardial ischemia* or *injury*, if there is adequate supporting evidence. In some cases the term "chronic" may be more appropriate than the term "old" to indicate the prolonged presence of active disease.

Terms	Approximate Time Range
Acute	Less than 3 days
Recent	Less than 1 month
Old	More than 3 months
Age undetermined	Unspecified

Frequency: Terms involving frequency are used with statements that describe recurrent features in the electrocardiogram, such as ectopic complexes. Ideally, the number of events should be stated in precise numbers per unit of time. The term "frequent" or "multiple" can be used if the feature occurs several times in a tracing mounted in a conventional manner. The term "occasional" can be used if it occurs only once or twice but is less advisable than stating the number.

Pediatric electrocardiogram: This report was prepared without the benefit of consultation with pediatric electrocardiographers, and the discussion is therefore limited to electrocardiograms of adults.[33–45] The terms used in pediatric electrocardiography are essentially the same as for the adult, but specific quantitative criteria and clinical correlations may differ in various pediatric age groups.

Vectorcardiography: Space does not permit inclusion of specific problems related to vectorcardiography. However, the technique differs from scalar electrocardiography in the display but not in the underlying theory or the data base.

Nomenclature versus criteria: In the following portions on contour and arrhythmias, emphasis is placed on nomenclature rather than on detailed, specific criteria. This approach appears desirable for the following reasons:

1. The proper application of the current knowledge and of the subsequent developments in electrocardiography depends on the availability of carefully chosen terms.
2. Although the electrocardiogram has been in use for almost a century, sharp boundaries between "normal" and "abnormal" have not been established. It does not seem appropriate at this time to recapitulate what is available in standard texts or review articles.
3. A meaningful list of criteria should be not only complete but also exhaustive and well founded and should include indications of their sensitivity and specificity. This would require a much larger Task Force and text.
4. Many criteria are more qualitative (morphologic) than quantitative (numerical) and would require illustrations to be meaningful. The number of illustrations that would be needed could not be incorporated within this report.

List of Standard Terms: Contour

Most Common Normal Variants

The following are the normal variants most often noted:[46–60]

Increased QRS amplitude: The term lacks precision because there are no precise values of upper limits of normal for each type of body build and chest wall thickness.

Low voltage: The term lacks precision because there are no precise limits of normal amplitude for different leads, different types of body build and variable chest wall thickness.

Abnormal amplitude of initial QRS deflection: These result in (a) abnormal Q waves (amplitude or duration) in one or more of the following leads: I, II, III, aVL, aVF, V_4 to V_6; (b) abnormal R waves (amplitude) in one or more of right and mid precordial V leads.

Prolonged Q-T_c interval: A corrected Q-T interval (QT_c) greater than 115 percent of normal without prolongation of the S-T segment, without increase in T wave amplitude or any other abnormalities. The pattern is sometimes due to neurogenic repolarization changes, but the clinical significance is frequently unknown.

S-T segment elevation: This may occur in one or more of the standard limb or chest leads as a normal variant, attributed to "premature repolarization."

Horizontal or depressed S-T segment: This is a rare normal variant with S-T segment depression ≤ 0.1 mv in one or more of the standard limb or chest leads, nearly always in women.

Inverted T waves in one or more of the right and mid precordial leads (V_1 to V_4): These are sometimes attributed to the persistence of "juvenile pattern."

Tall T waves: No upper limits of normal have been established.

Increased U amplitude: No upper limits of normal have been established, but the amplitude must be related to heart rate because U wave amplitude usually increases with increasing R-R interval.

Diphasic or negative U wave: If not exercise-induced, and not associated with other electrocardiographic abnormalities, this is frequently associated with left ventricular hypertrophy or coronary artery disease but occasionally occurs without obvious heart disease.

Notched QRS complex: This may be due to myocardial disease but frequently occurs in the absence of heart disease.

Poor R wave progression: This term is not precise, and its use is to be discouraged. If used, it should not be interpreted as evidence of myocardial infarction or other structural abnormalities.

Dextrocardia: The pattern in the limb leads is identical with reversal of right and left arm electrodes, but the pattern is characteristic in the precordial leads.

S1, 2, 3 pattern: This pattern may occur as a normal variant, particularly in young persons, but is sometimes present in patients with right ventricular enlargement or chronic lung disease.

Rotations: The outworn terms "clockwise," "counterclockwise," "apex forward" and "apex backward" rotation of the heart should be discouraged because they lack precise meaning and may be misleading.

Junctional S-T segment depression, J point depression, junctional depression: These terms are widely used to characterize deviation of the initial portion of the S-T segment from the baseline; such deviation is believed to be caused in many cases by atrial repolarization.

Chamber Enlargement (Hypertrophy)

Electrocardiographic diagnosis of chamber enlargement[61–92] is based on various wave form changes resulting from one or more consequences of hypertrophy, dilatation, conduction disturbance or change in chamber position. The criteria are not uniform, and the terminology is partly unsettled. For the atria, the preferred term is *enlargement*. The term *atrial hypertrophy* should not be used because there are no sufficient correlations between the electrocardiographic changes and atrial weight. For the ventricles, both *ventricular hypertrophy* and *ventricular enlargement* have been widely used. Although both terms have some advantages and some drawbacks, the term *enlargement* is preferred by the majority of Task Force members and consultants.

Left atrial enlargement: The criteria are based on P wave duration and alterations in the direction and amplitude of the terminal P wave vector. The specificity of these criteria is low. The term *P mitrale* should be discouraged because it may be misleading. The terms *left atrial overload* and *left atrial abnormality* have some proponents but no uniform acceptance.

Right atrial enlargement: The criteria are based on the increase in amplitude of the anteriorly directed P wave vector and the less specific inferiorly directed deviation of the P wave vector. The latter effect produces a pattern known as *P pulmonale*, a term widely used to describe a tall frequently peaked P wave of normal duration in leads II, III and aVF. Use of this term should be discouraged because a P pulmonale pattern may occur in the absence of both lung disease and right atrial enlargement, and it may be precipitated by such conditions as tachycardia, hyperthyroidism or low diaphragm position. It should be noted that the term *right atrial enlargement* is not always synonymous with *P pulmonale*.

The term *P congenitale* is to be discouraged. The terms *right atrial overload* and *right atrial abnormality* have some proponents but no uniform acceptance.

Left ventricular enlargement (hypertrophy): The diagnostic criteria include various combinations of the following changes: increased QRS voltage; posterior and sometimes leftward deviation of the mean QRS vector; increased duration of the QRS complex; delayed intrinsicoid deflection; widening of the QRS/T angle; and incomplete left bundle branch block.

Use of the following two terms should be discouraged: (1) *left ventricular strain*; this term can be replaced by the designation *hypertrophy* (or *enlargement*) with secondary repolarization abnormalities; (2) *left ventricular (systolic or diastolic) overload pattern,* because it lacks precision and sound electrophysiologic basis.

Right ventricular enlargement (hypertrophy): Several types of patterns may occur depending on the degree of enlargement and the clinical condition responsible for the anatomic change. The most common diagnostic criteria are based on the presence of one or more of the following changes: increased rightward anterior QRS vector (or decreased posterior QRS vector); increased rightward posterior QRS vector; complete or incomplete right bundle branch block; abnormal amplitude of the terminal QRS vector in a complete or an incomplete right bundle branch block; and right axis deviation.

Use of the following terms should be discouraged: (1) *right ventricular strain;* this term can be replaced by the designation *enlargement* (or *hypertrophy*) with secondary repolarization abnormalities; (2) *right ventricular (systolic or diastolic) overload pattern,* because it lacks precision and sound electrophysiologic basis.

Combined enlargement (hypertrophy): The term *combined* is acceptable as are the terms *biatrial* and *biventricular*.

Axis deviation: *Abnormal left axis deviation* and *abnormal right axis deviation* are acceptable terms; they should be used with caution in the absence of information about age, height and weight of the patient.

Septal hypertrophy: This term should not be used because criteria are not precise and the electrophysiologic mechanism underlying "abnormal Q waves" in certain patients with left ventricular hypertrophy (particularly obstructive cardiomyopathy) has not been clarified.

Myocardial Ischemia, Injury and Infarction

The manifestations of ischemic injury in the myocardium often produce sequential changes of varying degree.[93–112] The electrocardiographic interpretation of such changes should be correlated with other independent data and integrated into the total clinical picture.

Ischemia: This term is widely used by electrocardiographers to characterize abnormalities of ventricular repolarization, but there is no general agreement on the

morphologic criteria characteristic of "ischemia" because some electrocardiographers use the term to refer to S-T segment changes, some to T wave changes alone and others to both S-T segment and T wave changes.

Injury (subepicardial, subendocardial): This term is widely used by electrocardiographers to describe deviations of the S-T segment from the baseline (elevation, depression).

Nontransmural infarction: This term is widely used by electrocardiographers to describe ventricular repolarization changes without abnormalities of the QRS complex. The assumption is that the infarction does not involve the epicardial surface. The synonymous term *intramural infarction* is less desirable.

Transmural infarction: This term (see location list) is used in the presence of typical change in the direction (and usually duration) of the initial QRS vector. The assumption is that the infarction involves the epicardial surface.

The likelihood of infarction can be expressed in the following terms: (1) cannot exclude (<25 percent); (2) possible (25 to 49 percent); (3) probable (50 to 90 percent); and (4) characteristic of (>90 percent).

The localization of infarction is useful although it is not always precise. Pathologic studies show that the distribution of the lesions frequently is patchy. Locations based on the presence of Q wave (leads in parentheses) include (1) septal (V_1, V_2); (2) anterior (V_3, V_4); (3) anteroseptal (V_1–V_4); (4) lateral (I, aVL, V_5, V_6); (5) anterolateral (I, aVL, V_3–V_6); (6) inferior (a synonymous but less desirable term is diaphragmatic) (II, III, aVF); and (7) posterior (wide R wave in V_1–V_2).

The age of the infarction should be stated if possible in the following terms: (1) possibly acute; (2) probably acute; (3) characteristic of acute; (4) age undetermined, probably acute; (5) age undetermined; (6) age undetermined, probably old; (7) probably not acute; and (8) old. The less desirable but commonly used terms are *evolving, evolution, healing* and *subsiding.*

Ventricular aneurysm: This is a widely used term. The electrocardiographic criteria are not precise and the specificity is limited.

Terms To Be Avoided in Describing Ischemia or Infarction

Hyperacute: This may be a useful concept clinically to describe certain changes similar to those observed in the experimental laboratory, but the specificity is very low. The term implies an early stage of acute ischemia or acute ischemia and injury, and can be more precisely referred to in those terms.

Poor R wave progression: This is a nonspecific pattern, which frequently leads to incorrect diagnosis of infarction.

High lateral infarction and high posterior infarction: Use of these terms is discouraged because the power to localize with this degree of precision has not been borne out in postmortem data.

Coronary insufficiency: This is an ambiguous term, with widely divergent meanings and implication.

Acceptable Terms in Describing Infarction

Apical infarction: This term has merit because often inferior infarction slightly overlaps the apex and manifests itself in Q waves in leads V_3 or V_4 as well as in II, III and aVF. However, the term may be misleading because it has been used in the past to describe massive circumferential involvement of the entire apex.

Anterior-inferior (transseptal infarction): This is similar in meaning to apical. Q waves are usually present in leads II, III, aVF and in one or more of leads V_1 to V_4.

Posterolateral infarction: This is manifested by Q waves in leads I, aVL, V_6 and wide R waves in leads V_1 and V_2.

Segmental infarctions (such as basal segment of inferior wall or apical segment of posterior wall): These terms have a limited supporting data base derived from correlations with angiography and ventriculography, but wide use of such terms is not yet recommended.

Subendocardial infarction: Some elect to use this term in cases of subendocardial injury (S-T depression) with an upright T wave (in leads I, II or V_2 to V_6) in the presence of appropriate clinical findings, particularly when the changes persist for hours or days.

Drugs and Electrolytes

In referring to drugs and electrolytes,[113–125] *the following terms are acceptable:*

Digitalis effect: When appropriate, it may be possible to add: no evidence of overdosage; possible overdosage; probably toxic; toxic.

Quinidine effect: When appropriate, it may be possible to add: nontoxic; possible overdosage.

Procainamide effect: It may be possible to add: nontoxic; possible overdosage.

Phenothiazine effect: This class of drugs may produce minor nonspecific T abnormalities, and (rarely) prolonged Q-T_c and increased U amplitude (thioridazine more commonly than other drugs).

Hypokalemia (hypopotassemia): This term reflects low plasma potassium ion concentration; electrocardiographic changes tend to parallel the severity of hypokalemia.

Hyperkalemia (hyperpotassemia): Electrocardiographic changes tend to parallel the severity of hyperkalemia.

Hypocalcemia and hypercalcemia: These terms are used, respectively, to reflect changes of low or high plasma calcium concentration.

Use of the term *electrolyte imbalance* is to be discouraged because it lacks precision. Only these four electrolyte abnormalities (hypokalemia, hyperkalemia, hypocalcemia and hypercalcemia) produce diagnostically useful electrocardiographic changes.

Miscellaneous Abnormalities

Various abnormalities may appear in the electrocardiogram:[126–141]

Pulmonary embolism, or acute cor pulmonale: Other terms, right heart overload (acute) and right

ventricular strain (acute), are less desirable. The specificity of the electrocardiographic changes is low. Criteria include changes in heart rate, rhythm and P wave, QRS axis shifts, appearance of incomplete right bundle branch block and T wave abnormalities.

Pericarditis: If possible, it should be stated whether the condition is acute, subacute or chronic. Criteria are based on abnormalities of S-T segment, P-R segment and T wave.

Myocarditis: There are no precise criteria. Usually the T wave changes are similar to those in pericarditis.

Nonspecific (nondiagnostic) T wave abnormalities: This term should be limited to patterns without S-T segment abnormalities and without marked Q-Tc lengthening, as in "cerebrovascular pattern."

"Cerebrovascular pattern" (neurogenic T wave abnormality): This term usually indicates prolonged Q-Tc, abnormal T wave amplitude and polarity, occasionally abnormal U wave amplitude.

Nonspecific (nondiagnostic) S-T segment and T wave abnormalities: This term reflects a combination of abnormal initial and terminal repolarization abnormalities.

Postextrasystolic T wave changes and abnormalities: These may occur in one or a few complexes after a premature complex.

Tachycardia and posttachycardia T wave abnormality: The change is limited to amplitude and polarity of the T wave without S-T segment abnormalities.

Hypothermia: "Deep" hypothermia (temperature less than 25° C) can be recognized in the electrocardiogram by the presence of a characteristic slow, usually positive wave, called an Osborn wave, inscribed during the terminal QRS portion.[38] Moderate hypothermia (for example, that occurring after exposure to cold), can be frequently suspected in the presence of bradycardia and prolonged Q-Tc interval.

Electrical alternans: Alternans may involve single, several or all electrocardiographic deflections. It is commonly present in patients with a large pericardial effusion or cardiac tamponade.

List of Terms: Procedures

The electrocardiogram can be used to monitor an almost unlimited number of events or physiologic interventions.[142–152]

Exercise (Stress) Test

It is desirable to state the method (for example, treadmill, bicycle or atrial pacing) and the purpose (such as detection of myocardial ischemia, study of arrhythmia, evaluation of physical fitness or evaluation of treatment).

Widely accepted terms are as follows:

Normal exercise test: This is synonymous with a negative exercise test (for myocardial ischemia). Type of test, duration of test, heart rate response, blood pressure response and other pertinent observations and measurements are usually included in the report.

Abnormal exercise test: This is synonymous with a positive exercise test (for myocardial ischemia).

Borderline abnormal exercise test: Changes are close to the criteria for an abnormal test.

Unsatisfactory exercise test: Results are not amenable to evaluation. Reasons should be specified.

Junctional S-T segment depression: Normal variant assumed to be due to atrial repolarization.

Hyperventilation and Orthostatic Electrocardiograms

In many laboratories the routine electrocardiographic stress test is preceded by a tracing recorded after 30 seconds of vigorous hyperventilation with the patient in the recumbent position, and one recorded immediately after standing up. This is helpful in the evaluation of exercise-induced repolarization changes, particularly in the differential diagnosis of myocardial ischemia.

Electrocardiogram After Smoking and During Other Procedures

Under certain circumstances, the effects of various interventions on the electrocardiogram may be of interest. This may include monitoring the effects of intravenous administration of drugs, inhalation of drugs and breathing of various gas mixtures.

Long-Term Ambulatory Monitoring (Holter)

Several techniques have been developed to record continuously one or more leads on magnetic tape. Some systems have been designed to record only specifically preprogrammed cardiac events such as multiple premature beats, rate and atrioventricular deviations. It is acknowledged that the recognition of rhythm or conduction abnormalities is dependent on the proficiency of the technician analyzing the Holter tapes.

Terms for Cardiac Rhythm and Conduction[153,154]

Preferred Terms Referring Predominantly to Impulse Formation

Arrhythmia (dysrhythmia): This term refers to any cardiac rhythm that is not a regular sinus rhythm at a normal rate. Such a rhythm may be of either sinus or ectopic origin, and may be regular or irregular. An arrhythmia may be due to a disturbance in impulse formation or conduction, or both. Not every arrhythmia is pathologic. An example of physiologic arrhythmia is the respiratory variation of sinus rate (sinus arrhythmia).

Inherent rate: This is the rate at which the impulse formation usually occurs at a given pacemaker localization. *For the adult the following figures are thought to represent a rough guide:*

Sinoatrial (S-A) node	50–100/min
Atrioventricular (A-V) junction	40–60/min
Ventricle	30–40/min

Pacemaker: A fiber or a group of cardiac fibers initiating one or more activations. This definition does not take into account the various mechanisms that may be

involved in generating a cardiac impulse. The *primary pacemaker* is the sinoatrial node. *An ectopic or subsidiary pacemaker* is any pacemaker outside the sinoatrial node.

Bradycardia: Three or more consecutive impulses from the same pacemaker at a rate less than the lower limit of its inherent rate.

Tachycardia: Three or more consecutive impulses from the same cardiac chamber at a rate exceeding 100/min. The site must be specified.

Premature impulse (activation, complex, discharge): An activation that precedes the expected discharge of the prevailing rhythm. This applies to premature depolarizations, echoes, captures and manifest activation from a parasystolic pacemaker. Premature impulses may occur singly or in pairs. When three or more are recorded in succession, this is by definition a tachycardia. A premature impulse is usually of ectopic origin.

Escape (impulse): One impulse or two consecutive impulses (atrial, A-V junctional or ventricular) arising as a result of undue delay in the formation or arrival of the prevailing rhythm. (See also descriptions of escape rhythm and premature impulse.)

Escape rhythm: Three or more consecutive escape impulses at a rate not exceeding the upper limit of the inherent rate of that particular pacemaker. (See also descriptions of escape (impulse), accelerated rhythm, and inherent rate.)

Accelerated rhythm: Three or more consecutive impulses from the same pacemaker at a rate exceeding the upper limit of its inherent rate, but less than 100/min. In any specific case the rate and site of impulse formation should be indicated.

Interpolation: The phenomenon in which a premature impulse, usually of ectopic origin, occurs between two consecutive impulses of another pacemaker.

Fusion complex: Simultaneous or nearly simultaneous activation of either the atria or ventricles (atrial or ventricular fusion complex) by impulses coming from different directions. This results in an electrocardiographic complex that is intermediate in form between the pure complexes resulting from the differently originating excitation waves (see also description of capture).

Paroxysmal supraventricular tachycardia: A tachycardia usually characterized by an atrial rate of 140 to 240/min and by an abrupt onset and termination. It may or may not be associated with intact A-V conduction. Special electrophysiologic studies may elicit specific mechanisms, such as retrograde and anterograde pathways and sites of reentry.

Flutter: Rapid and regular electrical activity of atria or ventricles that is characterized electrocardiographically by the absence of an isoelectric line in at least one lead.

Atrial flutter: The rate of the atria is usually in the range of 250 to 350/min, and typically displays a sawtooth appearance in leads II and III.

Ventricular flutter: The ventricular rate usually exceeds 250/min, but the components of the QRS complex and T wave cannot be clearly identified or separated.

Fibrillation: Irregular, totally disorganized electrical activity of the atria or ventricles, or both.

Arrest: Cessation of electrical activity of the heart or a specific pacemaker. Arrest may be caused by different electrophysiologic mechanisms that should be defined if possible (for example, exit block of one or more impulses). (See description of exit block.)

Controversial or Nonprecise Terms

Wandering pacemaker: A rhythm characterized by gradual alteration of the P wave contours and sometimes cycle length.

Extrasystole: A premature impulse (S-A nodal, atrial, A-V junctional or ventricular) that usually shows a fixed relation to the preceding discharge of another pacemaker. The term is to be discouraged because it may not be an extra complex and does not always result in mechanical systole. However, the term is widely used in practice. (See also description of premature impulse and echo.)

Atrial flutter-fibrillation: This term implies some characteristics of atrial flutter and some of atrial fibrillation. Such a record is best classified as atrial fibrillation when the criteria of atrial flutter are not satisfied. It should not be mistaken for the alternation of atrial flutter and fibrillation in the same record.

Terms To Be Avoided

Bradyarrhythmia: Not a specific electrocardiographic term.

Tachyarrhythmia: Not a specific electrocardiographic term.

Beat: Use of this term in electrocardiographic nomenclature is inappropriate because it connotes the mechanical event after excitation of a cardiac chamber.

Depolarization: Decrease of membrane potential (less negative). Because depolarization occurs at a cell level, its use is best restricted to the description of the electrophysiologic phenomenon. In clinical electrocardiography, when referring to a deflection that represents the electrically active state of the myocardium, better terms are discharge, activation, excitation or impulse.

Paroxysmal atrial tachycardia: The specific role of the atria in the mechanism of paroxysmal tachycardia is difficult to determine without special electrophysiologic studies. (See description of paroxysmal supraventricular tachycardia.)

Paroxysmal A-V junctional or A-V nodal tachycardia: The same considerations apply as described in the preceding paragraph.

Nonparoxysmal tachycardia: What is meant in most cases is accelerated impulse formation.

Pseudofusion beat: Superimposition of an artificial pacemaker artifact on a spontaneous P wave or QRS complex. This indication serves no special purpose and creates confusion.

Idioventricular tachycardia: The term *accelerated ventricular rhythm* is preferred.

Terms Referring Predominantly to Impulse Conduction

Preferred Terms

Block: This refers to delay or failure of impulse propagation. Conduction disturbances of various degrees may occur in many different locations within the heart, and may reflect delay or failure of propagation in either the antegrade or retrograde direction, or both.

Intraatrial conduction delay: Conduction delay within the atria resulting in abnormal widening or distortion, or both, of the P wave.

First degree block: Delayed conduction within the heart with a 1:1 conduction ratio. In any individual case, the conduction time and site of delay should be specified when possible. (See also descriptions of second and third degree block.)

Second degree block: A conduction disturbance in which not every impulse is propagated from its site of origin. This conduction disturbance can be expressed as a conduction ratio. Second degree block is subclassified into type I, type II and advanced block.

Advanced (second degree) block: A form of second degree block in which either alternate or two or more consecutive impulses fail to be conducted. This includes 2:1, 3:1 and 4:1 block. (See descriptions of second and third degree block.)

Third degree block or complete block: Complete failure of impulse propagation usually associated with independent activation of the chamber distal to the site of block.

Intraventricular block: The anatomy and function of the intraventricular conduction system remain controversial. It is clear that there are two distinct bundle branch systems (right and left). The left bundle branch appears to consist of two groups of functioning fibers (fascicles), anterior and posterior. Several workers have also described groups of interconnecting septal fibers ("septal fascicles").

Accepted electrocardiographic patterns are described for block in the left bundle branch, the individual divisions of the left bundle branch, the right bundle branch, and the right bundle branch in combination with either division of the left bundle branch. The representation of block within the septal division of the left bundle branch lacks clearly defined criteria. The term *complete bilateral bundle branch block* implies *complete* interruption of the intraventricular conduction system with resultant complete A-V block. Confusion occurs in utilizing the terms unifascicular, monofascicular, fascicular, bifascicular and trifascicular block. It is recommended that conduction defects be described specifically in terms of the structure or structures involved (for example, "right bundle branch block with left anterior fascicular block," rather than "bifascicular block").

Fascicular block: This is an electrocardiographic (electrophysiologic) concept that ascribes certain wave forms to particular patterns of disturbed intraventricular conduction. (See also description of intraventricular block.)

Monofascicular block: See description of intraventricular block.

Bundle branch block: A conduction disturbance within one of the bundle branches (see also block). It may be complete or incomplete, permanent or intermittent, or unilateral or bilateral.

Bundle branch block, complete: This pattern indicates the absence of conduction in a bundle branch, or a delay of such magnitude that ventricular activation occurs largely or exclusively through the contralateral bundle; in adults this causes widening of the QRS complex to 0.12 second or more.

Bundle branch block, incomplete: This pattern often indicates delay in activation of the ipsilateral ventricle by way of that bundle branch, or sufficient delay to allow partial activation by way of the contralateral bundle.

Nonspecific intraventricular block: This applies to any type of intraventricular conduction disturbance that cannot be ascribed to block in a specific portion of the specialized conduction system.

Atrioventricular (A-V) dissociation: A descriptive term indicating at least two independent rhythms, one arising in the atria, the other in A-V junctional or ventricular tissues. *A-V dissociation is never a primary disturbance of rhythm but rather a consequence of a basic disorder of impulse formation or conduction.* It may be due to failure of impulse formation (default) or increase in the rate of the subsidiary pacemaker (usurpation). Dissociation may occur for single activations, or may last longer. In the presence of captures, dissociation is *incomplete.* When there are no captures during the time of recording, dissociation is considered complete. Dissociation should not be used as a synonym for complete A-V block, which may be one of the possible underlying mechanisms. (See also descriptions of block, capture and parasystole.)

Controversial or Nonprecise Terms

Hemiblock, left anterior and left posterior: These terms are synonymous with left anterior fascicular or divisional block and with left posterior fascicular or divisional block, respectively.

Periinfarction block: Specific conduction defects existing in the presence of myocardial infarction should be identified. The term periinfarction block implies conduction disturbance near the site of infarction. This can seldom be recognized with certainty.

Terms To Be Avoided

High degree block or high grade block: By definition, this is still a form of second degree block. Therefore, it seems appropriate to classify this conduction disturbance as *advanced second degree block.*

Intramural conduction disturbance: This term suggests a conduction disturbance within the ventricles, which causes a specific widening or slurring (or both) and notching of the QRS complex. In most cases, however, the exact site and extent of the conduction ab-

normality are not known. Therefore, the noncommittal term *nonspecific intraventricular block* is preferred.

Parietal block: This term is not descriptive of a specific site or type of conduction disturbance. (See description of intramural conduction disturbance.)

Arborization block: The term lacks specific meaning. (See description of intramural conduction disturbance.)

Interference: Rarely has a term created so much disagreement and confusion. Some have used it to indicate the short disturbance of the rhythmic action of one pacemaker by the activity of another (for example, resetting of a junctional or ventricular pacemaker by a ventricular capture during incomplete A-V dissociation); others have defined it as the expression of a physiologic mechanism, namely, delay or failure of impulse conduction due to induced normal refractoriness of a conduction pathway or the myocardium (collision of two impulses coming from the opposite or the same direction). For clarity, it is advisable to avoid the term interference.

Terms Referring Predominantly to Specific Mechanisms Operating in Arrhythmias

Preferred Terms

Parasystole: A rhythm consisting of dual activation of a single cardiac chamber in which one pacemaker (the parasystolic one) is protected intermittently or totally from discharge by the prevailing rhythm. At times two or even more parasystolic rhythms may coexist (*multifocal parasystole*).

Multifocal tachycardia (multiform): Supraventricular or ventricular tachycardia characterized by varying cycle length and configuration of atrial or ventricular complexes.

Coupling interval: The time interval between two impulses, usually an ectopic impulse and a preceding nonectopic impulse.

Conduction ratio: The ratio of the number of impulses that arrive at a site of block to the number that are propagated.

Aberrant conduction: The abnormal spread of an impulse through the normal or expected pathway, resulting in an altered electrocardiographic wave form from the chamber distal to the site where the impulse originates. Thus, aberrant conduction may occur within the ventricles or the atria. It is preferred to reserve this term for conduction delays within the normal pathway, thus excluding altered configuration due to preexcitation. Whenever possible, use of the term aberrant conduction should be related to a functional, rate-related mechanism underlying the altered spread of excitation.

Second degree block, type I (Wenckebach): Intermittent failure of impulse conduction in which the blocked impulse follows a number of impulses with varying degree of prolonged conduction relative to the first impulse conducted after the block. This may also be termed *Wenckebach periodicity* and *Mobitz type I block.*

Second degree block, type II (Mobitz, type II): Intermittent failure of impulse conduction following a number of impulses conducted without changes in their conduction time. The diagnosis of *Mobitz type II block* is supported by the finding of an unchanged conduction time of the impulse after the blocked impulse. (See also description of second degree block, type I.)

Anterograde or orthograde conduction: Conduction of a cardiac impulse in the direction of normal cardiac activation (from the atria to the ventricles).

Retrograde conduction. Conduction of a cardiac impulse in a reversed direction; the term is usually used to indicate ventriculoatrial conduction.

Entrance block: Delayed or failed penetration of an impulse into a pacemaking center. When an impulse fails to penetrate and reset (discharge) a pacemaker, the pacemaker is said to be protected. When there is delayed or only occasional resetting, protection is incomplete. (See also description of exit block.)

Exit block: Delay or failure of a pacemaker impulse to discharge surrounding myocardium. (See also description of entrance block.)

Ventriculoatrial (V-A) block: Delay or failure of an impulse to be conducted from the ventricles to the atria.

Capture: Usually premature activation of the atria (atrial capture) by a ventricular or junctional impulse conducted in retrograde fashion, or premature activation of the ventricles (ventricular capture) by a supraventricular impulse conducted in anterograde fashion.

Concealed conduction: Propagation of a cardiac impulse in such a manner that it influences subsequent events but does not manifest itself as a specific wave form.

Supernormal conduction: Conduction that is more rapid than expected.

Supernormal excitability: Activation resulting from a subthreshold stimulus, that at other times in the cardiac cycle fails to elicit a response.

Gap in A-V conduction: A period in the cardiac cycle during which an atrial impulse is not conducted to the ventricle, whereas earlier or later atrial impulses are conducted. This phenomenon can be seen in other tissues. (See description of supernormal conduction.)

Reentry: The phenomenon in which the same cardiac impulse enters a circuit and returns *to* or *toward* its area of origin. Reentry may result in one or more activations of the heart or cardiac region, but it may remain concealed. *Concealed reentry* may occur.

Echo: Return of an impulse to its site of origin.

Bigeminy: A repetitive pattern of two relatively closely spaced impulses, usually followed by a longer interval. (See also description of trigeminy.)

Trigeminy: A repetitive pattern of three relatively closely spaced impulses, usually followed by a longer interval. The third impulse ordinarily is a premature complex; less commonly, one sinus impulse is followed by two consecutive premature ectopic complexes.

Preexcitation: Excitation of a cardiac chamber, or part of it, earlier but not necessarily in a different

manner from what is expected. Thus ventricular preexcitation can be defined as excitation of the ventricles or a portion of the ventricles that occurs earlier than would be expected when the supraventricular impulse propagates through the normal A-V node-His bundle system. (See descriptions of Wolff-Parkinson-White and short P-R patterns.)

Short P-R interval (without delta waves): The P-R interval is shortened to less than 0.12 second (in adults), and there are no delta waves. There are many causes for this phenomenon.

Wolff-Parkinson-White (WPW) pattern: Preexcitation of the ventricles by means of an additional and abnormal anatomic A-V connection. In such cases, excitation by way of the accessory pathway will cause shortening of the P-R interval, a delta wave and widening of the QRS complex. Absolute values for P-R interval, delta wave and QRS width are variable. The electrocardiographic manifestations may be intermittent and the anatomic substrate for reentrant tachycardias may be present (although undetectable) in the routine surface electrocardiogram (concealed preexcitation). By definition, *Wolff-Parkinson-White syndrome* requires association with ectopic tachycardias.

Controversial or Nonprecise Terms

Atrial dissociation: A dual atrial rhythm in which independent activity in each atrial chamber can be established using special electrophysiologic techniques of recording.

Wedensky effect: This refers to an electrophysiologic observation of a subthreshold stimulus resulting in an effective activation when it is preceded at a given time interval by a suprathreshold stimulus, which itself results in an effective activation.

Wedensky facilitation: This refers to an electrophysiologic observation of a properly timed stimulus, which can cause dissipation of a conduction block for variable times.

Vulnerable period: A period during the cardiac cycle when stimulation or activation by a propagated impulse results in a repetitive response or fibrillation. The term is primarily used in the laboratory setting.

Circus movement: A phenomenon of repetitive reentrance in which the site is seldom discernible in the electrocardiogram. This is mainly an electrophysiologic term.

Terms To Be Avoided

Chaotic rhythm: This term is better avoided since it is difficult to define. (See description of multifocal tachycardia.)

Reversed coupling (return extrasystole): Resetting of the sinoatrial node by an ectopic atrial impulse or ventricular impulse conducted in retrograde manner. This causes a fixed time relation between the ectopic impulse and the following sinus discharge. However, considering the definition of coupling (see description of coupling interval), there seems to be no need for the term *reversed coupling*.

Antegrade conduction: See description of antegrade conduction.

Reciprocation: Continued reentry (circus movement) leading to several activations of a cardiac chamber. (See description of reentry.)

Reciprocal or reentrant impulse: See descriptions of reentry and reciprocation.

Lown-Ganong-Levine (LGL) pattern: A pattern characterized by a short P-R interval and normal QRS complex. The Lown-Ganong-Levine syndrome implies the presence of tachycardia.

Accelerated conduction: This term implies an electrophysiologic mechanism that has not been demonstrated.

Preferred Miscellaneous Terms

Cardiac electrogram: A unipolar or bipolar record of electrical activity of the heart, taken with the electrode or electrodes within a cavity of the heart or in contact with the myocardium (direct leads) (for example, intracavitary electrogram or epicardial electrogram). Cardiac electrograms can be further defined according to the position of the recording electrodes, that is, according to the proximity of the structure whose activity one wishes to record. Thus, intracavitary electrograms may be recorded from the right or left atrium (high or low), from the region of the atrioventricular (A-V) junction (A-V junctional electrogram), from the ventricles, and so forth. An A-V junctional electrogram may be labeled a *His bundle electrogram* (*HBE*) when a His bundle deflection is recorded.

Refractory period: The period in the cardiac cycle during which the conduction system or the myocardium (or both) demonstrates an altered response or no response to a stimulus.

Relative refractory period: That interval in the cardiac cycle during which the excitability threshold is higher and conduction is slower than during recovery (diastole).

Absolute refractory period: That period in the cardiac cycle during which the heart is not excitable.

Electronic Pacemakers

In describing the function of the pacemaker, the following observations should be made: pacing function (capture-noncapture, status of sensing) in both demand and fixed (magnetic) modes, configuration of paced complexes, pacing rate and interpretation of intrinsic or competing cardiac rhythms. The chamber paced is identified by V for ventricle, A for atrium, and D for double (both atrium and ventricle) (Table I).[155] The chamber sensed is again labeled V for ventricle, A for atrium. The mode of response, if any, is either I for inhibited, a pacemaker whose output is blocked by a sensed signal, or T for triggered, a unit whose output is fired by a sensed signal. The letter O indicates that a specific comment is irrelevant. Hence, the most commonly used pacemaker (ventricular-inhibited) would be designated VVI.

Complicated pacing systems can also be described functionally by no more than three letters. For example, when *two* pacemakers are implanted to achieve A-V synchrony, the ventricular pacemaker senses the atrial

TABLE I

Code for Identification of Pacemakers

1st Letter: Chamber Paced	2nd Letter: Chamber Sensed	3rd Letter: Mode of Response	Generic Description	Previously Used Designation
V	O	O	Ventricular pacing; no sensing function	Asynchronous; fixed rate; set rate
A	O	O	Atrial pacing; no sensing function	Atrial fixed rate; atrial asynchronous
D	O	O	Atrioventricular pacing; no sensing function	A-V sequential fixed rate (asynchronous)
V	V	I	Ventricular pacing and sensing, inhibited mode	Ventricular inhibited; R-inhibited; R-blocking; R-suppressed; noncompetitive inhibited; demand; standby
V	V	T	Ventricular pacing and sensing, triggered mode	Ventricular triggered; R-triggered; R-wave stimulated; noncompetitive triggered; following; R-synchronous; demand; standby
A	A	I	Atrial pacing and sensing, inhibited mode	Atrial inhibited, etc. (See VVI, but substitute atrial P wave for ventricular R wave)
A	A	T	Atrial pacing and sensing, triggered mode	Atrial triggered, etc. (See VVT, but substitute as in AAI)
V	A	T	Ventricular pacing; atrial sensing, triggered mode	Atrial synchronous; atrial synchronized; A-V synchronous
D	V	I	A-V pacing; ventricular sensing, inhibited mode	Bifocal sequential demand; A-V sequential

A = atrium; A-V = atrioventricular; D = double chamber; I = inhibited; O = not applicable; T = triggered; V = ventricle.

pacemaker that both stimulates and senses the atrium.

Format of the Electrocardiogram

The electrocardiographic report is a consultation for the use of physicians in patient management. The key factor is the competence of the interpreter, who should have adequate theoretical knowledge and practical experience. The electrocardiographer should be familiar with the fundamentals of cardiac electrophysiology, which include (1) the genesis of electric activity, that is, cardiac action potential; (2) the spread of activation; (3) properties of the volume conductor; and (4) lead system and recording apparatus. Further, the electrocardiographer should understand the principles underlying the role of the electrocardiogram in determining cardiac position, extracardiac influences, detection and localization of various acute, transient and permanent structural abnormalities, pharmacologic and metabolic effects, and analysis of events related to automaticity, conduction and refractoriness.

The electrocardiographic report should not include evaluations of functions that are beyond the scope of electrocardiographic analysis, such as hemodynamics, and should not contain unsupported statements about the presence or absence of heart disease.

Optimal formats for conventional electrocardiography and computerized electrocardiography may differ somewhat because of the technology employed. Many automated electrocardiographic processing programs are currently in existence[156] and, with further developments, more ways of arranging formats of display and interpretation can be expected.[157] Ideally, logic, clarity and practicality should supersede historical precedence, which now dominates the field. The format of the electrocardiogram to be described constitutes recommended guidelines rather than a rigid model for universal use. It may be modified in various ways to serve the specific needs of the users.

Electrocardiographic Display Format

Multichannel recording of several leads simultaneously is more advantageous than single channel recording, for the following reasons: (1) It allows more precise measurements of the onset and offset of deflections; (2) it captures transient events in multiple leads; (3) it provides better understanding of the activation and recovery process; (4) it facilitates production of several tracings, one of which may remain with the patient's record for the physician's immediate inspection; (5) in addition, it allows presentation of all data on a single sheet of paper, which can fit into a standard chart, thereby eliminating or simplifying the cutting and mounting.

A simultaneously recorded 12 lead electrocardiogram may be desirable; however, it is technically difficult at this time. With present techniques it is possible and practical to record three or six leads simultaneously, and obtain four sets of three leads or two sets of six leads, respectively, recorded sequentially.[158] Multichannel printouts are easily accomplished with computer techniques, but at this time telephone transmission of more than three channels is not uniformly available.

Lead Sequence

The usual sequence of recording for single channel machines is lead I, II, III, aVR, aVL, aVF, V_1, V_2, V_3, V_4, V_5 and V_6; with three channel machines, the same sequence is used in groups of three leads at a time. The three channel record is displayed with leads I, II and III aligned vertically, followed by leads aVR, aVL and aVF, then V_1, V_2 and V_3 and finally V_4, V_5 and V_6. Sometimes orthogonal vector leads X, Y and Z are recorded. Six

channel machines customarily record leads I, II, III, aVR, aVL and aVF vertically then leads V_1, V_2, V_3, V_4, V_5 and V_6. A different sequence for displaying the limb leads has also been proposed.[159] Occasionally, additional leads such as V_3R, V_4R, V_7 or leads made at higher or lower intercostal spaces are recommended.

Duration of recording: Complex to complex variations in electrocardiographic records due to cardiac or extracardiac effects make it desirable to display several cardiac complexes in each lead. Some computer programs use 5 seconds of data from each lead; this results in a 12 lead record, which occupies two conventional sheets of paper. Shorter records, using, for example, 2.5 seconds per lead, may not be as advisable for interpretation but can be displayed on a single sheet of paper along with an interpretive report. An additional continuous record (rhythm strip) is recommended when an arrhythmia is present; it should be recorded with leads that show prominent atrial activity, such as lead V_1. The rhythm strip should be at least 10 seconds in duration, and may be considerably longer in cases with intermittent or complex rhythm disturbances.

Report

Whenever practical, it is desirable to place the electrocardiogram and the basic components of the report on the same sheet of paper. The report consists of (1) identifying data, (2) essential measurements, (3) description, and (4) interpretation.

Identifying data: Each electrocardiogram should be identified with the patient's name, patient identification number if available, and the location, date and time of the recording. To minimize the possibility of error, this information should be placed on each sheet of the record immediately after completion of recording. The addition of a code number identifying the technician and recording instrument is recommended for quality control. The minimal patient information required for electrocardiographic interpretation includes age, sex and history of cardiac medications. The absence of this information seriously hinders preparation of a definitive report. Other information useful for interpretation are race, body build, blood pressure, tentative clinical diagnosis, clinical status (preoperative, for example) and noncardiac medication such as phenothiazines that may affect the electrocardiogram. The body build may be described by height and weight measurements, but if these are not readily available, a code may be used to identify body build (obese, slender, and so forth). Observations by the technician concerning an unusual position of the patient during the recording procedure (for example, sitting), or presence of thoracic deformity, amputation, respiratory distress or muscle tremor should be included in the report.

Measurements: Measurements should include atrial or ventricular rate, or both, and P, P-R, QRS and Q-T (Q-Tc) intervals. The mean P, QRS and T axes may be included. In some formats, electrical position is included under measurements or description.[160]

Description: The description of the various components of electrocardiographic complexes, if relevant to establishing the criteria for interpretation, should be made in logical order from P to U waves. The relevant changes from previous tracings should be indicated.

Interpretation: This should include (1) statements concerning the rhythm (for example, sinus rhythm with ventricular premature complexes); (2) diagnostic statements; (3) comparison with previous tracings; (4) comments; and (5) classification statement.

If the technical quality of the electrocardiogram is not satisfactory, the report should state the reasons (for example, incomplete electrocardiogram, baseline wander, noisy tracing, artifact present, muscle artifact, 60 hertz artifact, poor frequency response, overdamped, underdamped, incorrect mounting, upside down lead or leads, mislabeled lead or leads, calibration absent, calibration error [specify in millimeters per millivolt]).

Diagnostic statements may describe specific cardiac disease, such as inferior myocardial infarction, or unusual findings that do not have a known relation to pathologic states, such as nonspecific (nondiagnostic) T wave changes. The most likely cause or causes of electrocardiographic features may be added whenever feasible.

Comments reflecting the interpreter's impression are useful at the end of the report: These include, when pertinent, recommendations for serial studies or special studies.

Classification: The classification should summarize the interpreter's overall impression of the measurements, description, rhythm and changes. The record may be classified as normal, abnormal, borderline (probably normal), borderline (probably abnormal), atypical or normal variant. From a practical standpoint, such classification is very helpful to the nonelectrocardiographer.

Physician identification: The report should identify the physician who prepared or reviewed the record.

Summary and Conclusions

The format of the electrocardiogram and the report must be comparable in quality to a consultation, but the format may be tailored to the specific needs of the user. The report may be arranged differently and may be omitted or combined. In the final analysis, the aim of the electrocardiographic report is to assist the clinician in managing the patient.

The use of standard terminology, criteria and format should decrease variability and error in interpretation and communication of electrocardiographic information. This should be true regardless of whether the information is conveyed in a computer report or in consultation between physicians. We recommend the best standards available at the present time and development of additional ones as indicated. We also recommend that a project to identify criteria for electrocardiogram-based statements be completed as soon as feasible, and that collection of a data base for evaluation of criteria requiring nonelectrocardiographic confirmation be continued and expanded.

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Task Force 1A: Development of a Data Base for Electrocardiographic Use

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Although considerable effort has been expended to develop criteria and terminology for standardized electrocardiographic analysis, controversy remains. Much of this controversy results from failure to reach agreement on widely acceptable electrocardiographic criteria for defining cardiac abnormalities. To assess the correlation between cardiac abnormalities and electrocardiographic findings it is essential to have extensive independent data.

The goals of this Task Force were to determine what independent data are necessary to establish diagnostic criteria and validate electrocardiographic interpretations. Additionally, there was an attempt to provide a data exchange format that would also be useful for collection, storage and retrieval of these data.

Objectives

The reasons for establishing protocols and collecting a large data base can be summarized:

1. To improve existing and define new electrocardiographic criteria
2. To provide support for better standardization of criteria and terminology
3. To improve communication and teaching of physicians and allied health personnel
4. To enhance present and future programming efforts to develop standards for computer electrocardiographic program testing and validation
5. To promote collaborative clinical research among institutions by employing compatible techniques in data collection

To meet these needs the design features of the data base should be specific enough to provide a means to test, validate and improve electrocardiographic diagnostic programs and yet be general enough to encourage basic and clinical electrocardiographic research.

This Task Force has identified several methodologies that may be used to conduct comparative evaluation of electrocardiographic programs and has taken the position that program evaluation should be delayed until methods of evaluation are better defined and agreed upon. To accomplish these goals it is important to establish clinical protocols to improve electrocardiogram-independent criteria.

This task force also divided electrocardiographic interpretations into three different categories:

A. Statements documented by electrocardiogram-independent data (hypertrophy and infarction, for example)

B. Statements based upon electrocardiogram-dependent criteria (arrhythmias and conduction disturbances, for example)

C. Purely descriptive statements that do not imply a specific diagnosis (axis deviation and certain repolarization abnormalities, for example)

The development of a data base for electrocardiographic use should be oriented initially to provide improved criteria for statements that the Task Force, considering the role of computers, has included in Category A.

General Guidelines for Data Base

The establishment of specific protocols for electrocardiogram-independent data should be structured to encourage collaboration among several institutions. Our purpose is to define the data for collection but not to identify the computer file structure or retrieval methods

to be employed. *General features of the data base should include:*

1. Common means of coding, identifying, and selecting patients
2. Machine readable and readily retrievable data that are interchangeable among institutions
3. Well defined objective quantitative data measurements and recording
4. Minimizing of investigation and variability by limiting subjective impressions
5. Mechanisms for quality control and periodic data review for accuracy and completeness
6. Techniques that assure patient privacy
7. Data collection techniques that interface with other ongoing studies whenever possible

Identification and Justification for Electrocardiogram-Independent Data

There is general agreement that the data base should include, but not necessarily be limited to, information of three basic types:

I. Historical data
II. Clinical measurements
   A. Coronary care unit
   B. Laboratory
   C. Echocardiography
   D. Cardiac Catheterization
III. Autopsy data

These specific categories were selected for the data base because they are commonly available, are meaningfully correlated with electrocardiographic abnormalities, can be best quantitated and reproduced and represent information most likely to reflect specific cardiac pathology.

Summary of Data Base Format

To determine the content necessary for an electrocardiogram-independent data base the Task Force examined several data collection forms from on-going collaborative studies in the United States and Canada. The design of each section within the protocol reflects the specific information considered important for the shared data base although each collaborative institution may use any format desired for its own data collection and storage. The data base protocol is assembled into three general categories: (I) historical data; (II) clinical measurements; and (III) autopsy data. The data sources included in the clinical measurements are limited to four: (A) coronary care unit; (B) laboratory; (C) echocardiography; and (D) cardiac catheterization.

The information requested in the history section is quite broad. However, it is considered important because of the potential influence upon a given electrocardiographic interpretation. The details included in the coronary care unit and laboratory sections are essential to confirm or exclude certain specific cardiac diagnoses. The measurements in each of the other sections—echocardiography, cardiac catheterization and autopsy—are sufficiently detailed and quantitative to provide in-depth information. The autopsy measurements have been selected to be most appropriate in relation to the clinical variables recorded in the other categories.

Conclusions and Recommendations

This task force makes the following conclusions and recommendations:

1. It is necessary to establish more objective electrocardiographic criteria for cardiac pathology. For basic and clinical research in electrocardiography to provide improved interpretations, comparison of electrocardiogram-independent data with electrocardiographic diagnoses is necessary.
2. An electrocardiogram-independent data base from several collaborating institutions should be encouraged. The Bethesda Conference in conjunction with the electrocardiographic Committee of the American Heart Association should recommend funding to support such a national data base collection.
3. It is necessary to review periodically the electrocardiogram-independent data base necessary for electrocardiographic evaluation and validation.

It is recommended that an ad hoc committee of the American College of Cardiology and the American Heart Association be established to encourage data base studies (and funding for such studies) and to review periodically the data base requirements for electrocardiographic research. This ad hoc committee should coordinate the implementation and ongoing effort of data collection.

Task Force II: Quality of Electrocardiographic Records

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In dealing with the quality of electrocardiographic records, we have attempted to identify and recommend the best accepted practices without making cost-effectiveness comparisons. Electrocardiographic quality begins with the skill of the recording technician, and we have examined means of developing this skill. It is dependent upon the fidelity of the recording and transmitting hardware, which we have evaluated. The efficiency and accuracy with which the electrocardiogram can be put to clinical use is dependent upon recording and ancillary data format. Storage and retrieval of electrocardiograms and ancillary data are required to

provide continuity of quality electrocardiography. The culmination of the electrocardiographic process is the clinical interpretation of the tracing. The medical and legal responsibilities of those concerned with electrocardiographic interpretation were explored.

In recommending any practice or process, we have sought the best recognizable state of the art consistent with established reliability. Where available evidence reveals no clear method of choice, we have attempted only to report this fact, sometimes with comment.

The quality of electrocardiograms and of their interpretations in daily practice is a representation of the extent to which theoretical electrocardiographic understanding and contemporary technology have been applied to clinical medicine.

Technician Training

An essential step in good electrocardiography requires that proper technique be consistently employed by technicians. Although newer electrocardiographs are more able to compensate for poor technique, technicians need some skill.

Prior Experience

An electrocardiographic technician need not have had prior professional experience. Any person of average intelligence can be taught to record high quality elective electrocardiograms during rest. We recognize that there are different levels of requirement, from technicians with minimal skill in exercise electrocardiography to experienced technicians in cardiac laboratories who, besides recording electrocardiograms at rest and during exercise, interpret Holter monitoring data and record other noninvasive cardiac performance measurements. On-site training in these laboratories is probably the most efficient way of producing electrocardiographic technicians of high caliber.

Training Requirements

As a minimal requisite, all electrocardiographic technicians should have a core training instruction that includes knowledge of the following:

1. Artifacts due to (a) improper electrode application; (b) powerline interference; (c) muscle tremor; and (d) peculiarities of the specific electrocardiograph in use.
2. Proper format of recording.
3. Recognition of patterns that require additional electrocardiographic recording.
4. Basic tests of performance of the electrocardiograph to include a check on proper paper speed and calibration pulse.

Electrode application: Instruction in electrode application should include knowledge of:

1. The proper position for standard 12 lead recording and optional lead systems (see record format). The use of devices for proper location of chest leads[1] is encouraged.
2. Proper skin preparation.
3. Recognition of artifacts due to lead reversal, loose electrodes or improper lead cable attachment.

Powerline and other types of artifact: Electrocardiographic technicians should learn to recognize alternating current interference. They should also be taught the common causes of such artifacts and methods for correcting them.

The causes of muscle tremor and ways of recognizing artifacts due to such tremor and of correcting them should be taught. Other causes of electrocardiographic artifact (coughing, respiratory variation, and so forth) should be illustrated during training of technicians.

Operation of specific electrocardiographs: Technicians should use manufacturers' instruction booklets for use and maintenance of specific machines. These instructions should be carefully explained by the training staff.

Recording format: The particular recording format in use should be explained to technicians, with provision of a checklist to ensure correct reading of *all* data.

Electrocardiographic interpretation: It is desirable that technicians have a summary understanding of the genesis of electrocardiographic waves so as to recognize arrhythmias requiring extra recording and the presence of lead switch applications and "alert" situations for an electrocardiographer.

Test of performance of the electrocardiograph: Technicians should be taught to recognize overdamping, underdamping, sensitivity setting and decay rate acceptability. They should be able to recognize signals indicating that manufacturer maintenance checks need to be carried out.

Form of Training

Training should be on-site for most purposes. In research studies, specific group instruction is mandatory for uniformity. Training manuals[2] have been published and also are produced by some manufacturers.

Examples of poor quality tracings, with their cause and correction, should be available. Electrocardiographic technicians' societies should be encouraged to provide such examples. Minimal acceptable limits (as described under "Record Format") should be adhered to.

Before commencing routine electrocardiograms, technicians should submit 5 to 10 tracings recorded by themselves to be "certified" by the local electrocardiographer.

Continuing quality control: Continued production of good electrocardiograms is best achieved by immediate feedback from electrocardiographers who have to interpret the tracings. As to the use of computer-read electrocardiograms, programs to detect records of unacceptable quality can be used to relay the same information. Apart from immediate feedback, a periodic summary stating the proportion of poor-quality tracings can be used to determine whether retraining is necessary. For such feedback, therefore, each technician should write his or her identification number on each record.

Record Format

Number of electrocardiographic channels: The single channel electrocardiograph has the lowest purchase price and smallest size; for these reasons, it is usually preferable for portable use and for use in physicians' offices and small hospitals.

Three simultaneous electrocardiographic channels allow superior interval measurements as well as time-coherent measurement of wave form vectors. Standard instrumentation exists for transmitting three simultaneous channels by telephone and radio; this number of channels may be simultaneously recorded on the most modestly priced instrumentation tape recorders. Existing three channel electrocardiographic recording facilitates visual interpretation of the tracing by the use of automatically formated records. Therefore, automatic three channel recorders will be preferred by most users who record a sufficient volume of electrocardiograms to justify the higher purchase cost of three channel equipment.

TABLE I

Lead Nomenclature

Electrode	Location of Attachment[8]
Right arm (R)	Right wrist
Left arm (L)	Left wrist
Left foot (F)	Left ankle
Right foot (G)	Right ankle
V_1	Right sternal margin, 4th intercostal space
V_2	Left sternal margin, 4th intercostal space
V_3	Midway between V_2 and V_4
V_4	Left midclavicular line, 5th intercostal space
V_5	Left anterior axillary line, V_4 level
V_6	Left midaxillary line, V_4 and V_5 level
V_7 and V_8*	Left posterior axillary line and left midscapular line, V_6 level
Leads* recorded on right side of thorax, such as	V_4R-right midclavicular line, 5th intercostal space

* Optional leads.

Number of leads recorded for resting electrocardiograms: A standard resting electrocardiogram should contain a minimum of the 12 conventional leads (3 Einthoven limb leads,[3] 3 augmented unipolar limb leads and 6 Wilson chest leads).[4] The additional recording of the Frank orthogonal leads[5] or some other combination of leads is optional.

Sequence of lead recording: Einthoven limb leads should come first, in numerical order, followed by augmented unipolar limb leads (aVR, aVL, aVF sequence), followed by the precordial leads in numerical sequence. These should be followed by the optional leads. When lead V_4R[6] is recorded, it may be inserted wherever desired in the sequence; however, it must be appropriately marked. For strictly practical considerations,* we recommend that lead V_4R be located in the position usually occupied by lead V_4 when automatic three channel electrocardiographs are used.

Nomenclature: The lead nomenclature recommended by the American Heart Association[7] is used to identify each lead: I, II, III, aVR, aVL, aVF, V_1 to V_6 and V_4R.

Location of electrodes: The electrodes for recording the standard resting 12 lead electrocardiogram are located according to Table I.[8] The precordial (V) electrodes (but not the limb electrodes) are located as shown in Figure 1. Location of electrodes for stress testing are described in Table II.

When it is impractical to attach electrodes on one or both wrists or ankles, this fact should be noted on the record and the electrode or electrodes attached more proximally on the limbs as necessary. If it is impractical to attach chest electrodes at their exact locations but it is possible to attach them within one interspace width of the correct location, this is permissible provided the details of the translocation are furnished with the tracing. Otherwise the affected electrodes are not attached and the reason therefore recorded and furnished with the tracing.

Length of leads recorded: 1. *For wave form interpretation,* a minimum of 2.5 seconds of recording is required, provided satisfactory technical quality of recording prevails.

* By displacing only one electrode instead of four, the likelihood of error in electrode positioning is minimized. That situation applies when the lead V_4 electrode is simply put on the right side of the chest contrasted with the situation required if all four electrodes, V_1 through V_4, are specially positioned to accommodate lead V_4R.

TABLE II

Some Bipolar Leads Used in Conjunction With Stress Testing

Lead	Positive Electrode Location	Negative Electrode Location	Comments
CM_5*	V_5 position	Manubrium	One of the most sensitive bipolar leads for detecting S-T changes
CH_5	V_5 position	Forehead	Favored in Sweden, especially for bicycle tests
CS_5	V_5 position	Right infraclavicular fossa	Detects somewhat more muscle artifact than lead CM_5
CC_5	V_5 position	V_6R position	Bears a closer resemblance to lead V_5 than most bipolar leads
CB_5	V_5 position	Low right scapula	Closely resembles lead V_5 but has more muscle artifact than most other bipolar leads
CR_5	V_5 position	Right arm	Used in northern Europe and USSR for pre- and postexercise records, usually with 4 to 6 chest lead positions. High muscle artifact level during exercise

* The number 5 refers to the position on the chest of a corresponding V lead such as V_5. Thus the positive electrode could be located in any numbered V lead position.

TABLE III

Electrode Locations for Exercise

Electrode Designations	Location on Body
	Frank Lead System, Exercise Modification*
A	Left midaxillary line, level of 5th interspace at the left sternal border
C	"45 point," level of 5th interspace at the left sternal border
E	Center of breastbone (sternum), level of 5th interspace at the left sternal border
F	Left lower abdomen (near anterior superior iliac spine)
G†	Right lower abdomen (near anterior superior iliac spine)
H	head (forehead); located near one side of the forehead near hairline
I	Right midaxillary line, level of 5th interspace at the left sternal border
M	Middle of back, level of 5th interspace at the left sternal border
	12 Lead Electrocardiogram, Exercise Modification
F	Left lower abdomen (near anterior superior iliac spine)
L	(Left arm), lateral aspect of left infraclavicular fossa
R	(Right arm), lateral aspect right infraclavicular fossa
V_1	Fourth interspace, right sternal border
V_2	Fourth interspace, left sternal border
V_3	Midway between lead V_2 and V_4
V_4	"45 point," level of 4th interspace at the midclavicular line
V_5	Midway between lead V_6 and V_4
V_6	Left midaxillary line, same horizontal level as lead V_4

* We recommend the modification employed by the Lipid Research Clinic Project, using the Frank electrodes designated A, C, E, I, M, H and F

† Patient ground.

2. *For rhythm interpretation,* a minimal continuous recording of 6 seconds is required.[9] This will permit recognition of the vast majority of cardiac rhythms, but in special instances, and particularly for the less commonly recognized arrhythmias, much longer records will be elected.

3. *For computer interpretation,* the length of record will be specified by the particular computer program used. To collect records for future computer analysis and to assure compatibility with all systems in current use, a minimum of 10 seconds of recording of each lead group is required, because current interpretive program requirements range from slightly more than 2 seconds to 10 seconds per lead group.[10]

Standardization: A 1 mv calibration pulse should be inserted at the beginning or at the end of the conventional 12-lead sequence. If the entire electrocardiogram is not recorded at the same deflection sensitivity, the exact sensitivity of each portion of the recording should be indicated appropriately.

Tracing quality: This includes the correctness of the identification data and of the clinical information furnished with the request for an electrocardiogram, as well as the date and time of recording. This also includes correctness of electrode application, baseline stability, baseline "jiggle," muscle artifact and powerline artifact (see Appendix I). Also affecting tracing quality are the qualities of the electrocardiograph (dealt with elsewhere), especially the fidelity of chart paper transport speed, stylus deflection accuracy and linearity, overall frequency response and common-mode rejection.

Ancillary patient data: It is recommended that ancillary patient data accompanying the electrocardiogram include the name of the subject, age, sex, race, drugs being taken, electrolyte status if known, height, weight and clinical diagnoses. These items constitute prior probability patient data that may enhance interpretation of the electrocardiogram both by certain computer programs and by human electrocardiographers, and therefore these data should be supplied with the request for the electrocardiogram.

Exercise Test Records

Preexercise Records

The resting control electrocardiogram should be recorded immediately before exercise and interpreted before proceeding with the test. It should be recorded at least 2 hours after eating, drinking or smoking, except under special test circumstances, and should include at least 12 conventional leads, optionally the Frank leads, and whichever lead pattern will be used for recording during and after exercise. The resting control electrocardiogram is recorded with the patient in the recumbent position, the standing position and in the position (such as sitting) used during the postexercise period. The mimimal time for recording the exercise electrocardiographic pattern is 5 seconds for each record. This shall not be construed to place any special limits on the record length requirements of computer analytical systems for the exercise electrocardiograms.

Exercise Records

The exercise lead pattern should consist of at least two simultaneous leads and preferably three leads. There is not sufficient information available to make a definitive requirement concerning the number of leads to be recorded during and after exercise, although persuasive data indicate that the more leads recorded, the greater the resulting test sensitivity.[11,12] Conventional Wilson V leads are preferred, but if bipolar leads are used, at least one should be lead CM_5, and no other leads should share the CM_5 precordial electrode. This procedure is used to ensure the maximal amount of diagnostic data acquisition from the exercise test, but also as a fail-safe technique to avoid loss of both electrocardiographic leads during the exercise test as the result of a single electrode failure.

Electrode locations: The locations of electrodes for some commonly used electrographic lead systems[13] are shown in Table II and Figure 1. The Frank lead system is described in Table III.

Hyperventilation electrocardiogram: This is strictly an optional record, but if used it should consist of at least a 5 second record of the electrocardiogram before and after the hyperventilation maneuver.[14] Be-

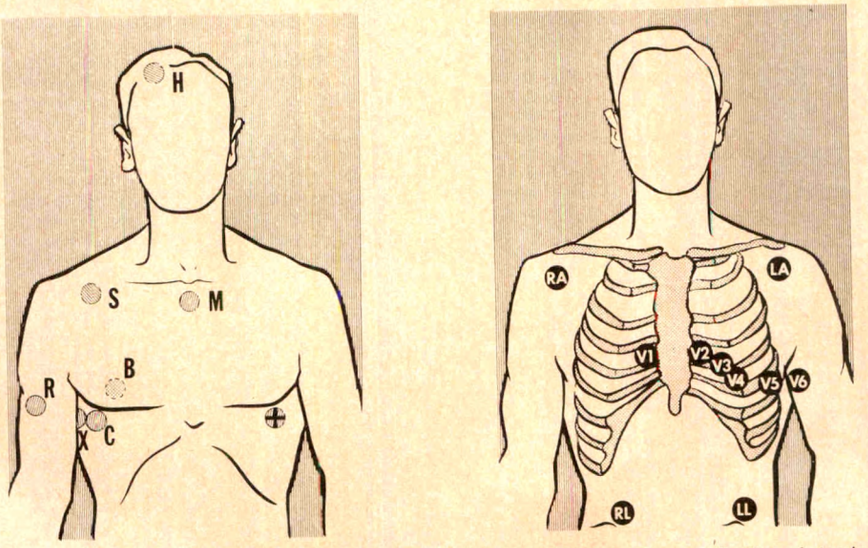

FIGURE 1. Electrode locations. **Left,** for bipolar precordial leads. **Right,** for the Mason-Likar exercise modification of standard electrocardiographic leads. B = back over low right scapula; C = V_5 position on right side of chest; H = head; LA = left arm; LL = left leg; M = manubrium; R and RA = right arm; RL = right leg; S = right infraclavicular fossa; + = V_5 position.

TABLE IV

Electrocardiographic Storage Media

Electrocardiographic paper
Wax-treated paper requiring a hot stylus recorder
Thermochemical-treated paper requiring a hot stylus recorder
Permeable ceramic-coated paper requiring direct contact with ink jets under high pressure
Untreated paper requiring ink jet or carbon-transfer recorders
Xerographic paper reduction of the electrocardiogram
Microfilming
35 mm on aperture cards
16 mm film in rolls or in microfiche jackets
Analog
Reel-to-reel tape
Cassettes
1/2 inch (1.27 cm) tape on Hollerith cards
Digital
Digital tape system
Floppy disc
Disc pack
Bubble memory (for the future)

fore studies proceed, these two records should be interpreted and any changes resulting from hyperventilation should be allowed to subside before exercise is continued.

Electrocardiographic recording during exercise: A continuous display of two or more leads by means of cathode ray oscilloscope should be displayed throughout exercise. Hard copy of recordings of at least 5 seconds' duration should be made every 3 minutes during exercise, with every change of work load, upon the appearance of any significant subjective or objective change in the test subject and upon the appearance of any significant change in rhythm or QRS-T contour during exercise, whichever occurs first, and at the end of exercise.

Postexercise electrocardiogram: A conventional 12 lead electrocardiogram should be recorded immediately after exercise with the patient in the same body attitude as for the preexercise control record. If the full 12 leads were not those chosen for in-exercise monitoring, then it will not have been necessary to use extensive skin preparation for all the involved electrodes, as is required for those electrodes generating the in-exercise electrocardiograms. This 12 lead electrocardiogram and the exercise monitoring leads, if different, should be repeated between 2 and 3 minutes after exercise and between 4 and 6 minutes after exercise. Electrocardiograms may be recorded more frequently if desired. The time of recording with respect to termination of exercise should be written on each record.

Postexercise recordings typically cease 6 minutes after exercise, but should extend until the electrocardiogram has stabilized for up to 10 minutes if significant changes occurred.

This Task Force believes that there is an excessive number of variations in the way exercise electrocardiographic testing is carried out. These include variations in the leads chosen for recording during and after exercise, in the mode of exercise used, in the protocol used to adjust work loads and time individual work loads, in the indications for terminating the exercise stress (and, consequently, in what constitutes an adequately diagnostic exercise test procedure) and, finally, in the interpretation of the resulting electrocardiograms because of variations in both the criteria used and the rigor with which electrocardiographic changes are measured.[7] These variations should not be discouraged in clinical investigations aimed at establishing which methods of stress testing are superior for application to a particular problem, but the wide variation found in the clinical practice of exercise testing has unnecessarily restricted the diagnostic potential of the test method. This Task Force urges that a scientific basis be developed for standardizing methodology of the exercise electrocardiogram. When rigorous comparisons demonstrate clear superiority of a particular technique, this technique should be recommended for general adoption except when investigational aims call for variations.

Other Forms of Electrocardiographic Recording

In addition to rest and exercise electrocardiography, many other clinical uses are made of the electrocardiogram. Long-term ambulatory electrocardiographic monitoring, intensive care unit and operating room electrocardiographic monitoring and supplementary electrocardiographic recording on phonocardiograms, echocardiograms and cardiac catheterization records of pressures and electrograms are the most common additional uses. We recognize the importance of all of these uses but do not believe that sufficient experience has been accumulated to make standardization of their format necessary or desirable.

Storage of Records

Duration of Storage

Because of the importance of serial electrocardiographic changes, an electrocardiogram should be kept for at least 5 years and representative tracings for as long as possible thereafter. We recommend that every electrocardiographic interpretation be kept indefinitely. Storage and retrieval capabilities should be maintained so that copies of electrocardiograms or their interpretations can be forwarded to other medical facilities, with the patient's consent. In conjunction with any storage technique, a clinical interpretive code with diagnostic criteria is advisable, such as that developed at the University of Utrecht.[15] When electrocardiograms are stored for future retrieval, distortion and the effects of aging should be avoided or minimized in whatever storage medium is used. The available storage media are listed in Table IV.

Electrocardiographic Storage on Paper

Since cutting and mounting can be avoided by the use of three channel electrocardiographs, it is often now economical and advantageous to obtain two or more 12 lead tracings 8 by 10 1/2 inches (20 × 27 cm) at the bedside and to use one for filing and another for the patient's record. The longest experience has been with wax-treated paper, which is known to retain an electrocardiographic image for 20 years or longer. However, it is pressure-sensitive and easily marred. This can be alleviated somewhat by covering the paper with plastic tape, but this adds to expense and technician time. The thermochemical-treated paper is newer, sturdy and not easily marred. There are many different types of thermochemical paper, and consequently data are not available regarding the

life expectancy of electrocardiographic images on it. The ceramic-coated paper is very sturdy and comparable in price. It has a hard ceramic finish with a high contrast, which makes it durable and easy to interpret. The untreated paper is the cheapest, but the ink-jet and carbon-transfer technique record characteristically "fuzzy" electrocardiographic images. The ink-jet[16] and carbon-transfer recorders are available with up to eight channels and are expensive; however, they have an excellent upper frequency response for phonocardiography and are very popular in Europe.

Blues and reds are poorly copied by some xerographic reproduction machines. Also, the symmetrical grid of the electrocardiographic paper can be distorted. Nonetheless, with proper equipment, long-lasting file copies of electrocardiograms of excellent quality and their interpretations can be quickly and economically made.

Electrocardiographic Storage on Microfilm

Microfilming is a good primary storage medium or a parallel technique to use with computerized storage.[17] Because it is impractical to transform paper-recorded electrocardiograms into an analog or digital format, microfilming will continue to be a valuable storage technique. There are many choices in microfilming methodology, but the best and cheapest technique has not been established. With available equipment, 35 mm reproductions can be copied, developed and mounted on aperture cards in 1 minute by untrained personnel. These Hollerith cards with a 35 mm aperture for the 35 mm film can be keypunched with identification information and sorted. The 16 mm reproductions must be filmed in rolls for economical development and take at least 2 days. They usually require cutting and insertion into microfiche jackets or expensive equipment so that particular electrocardiograms may be located in the microfilm roll cassettes. Microfiche jackets have many advantages, including retention of up to 60 records, inexpensive duplication, easy scanning, and at least a 24 to 1 reduction in storage volume. Many medical data bases are being maintained in this medium, and it appears to be inexpensive and convenient. Additional rolls of microfilm are easily and economically established for security. With any microfilming technique, care must be taken to see that archival capabilities are maintained by removing less critical data achieving the proper density, and caring for the film properly. Microfilming techniques require microfilm readers and copies in strategic, convenient locations. Currently, the 8 by 10 1/2 inch paper reproductions of microfilm images are expensive and of poor quality.

Magnetic Storage of Electrocardiographic Records

Compression schemes[18] for analog or digital electrocardiographic storage must be extensively verified by independent institutions or organizations before they are accepted. These compression techniques are necessary for economical storage but can result in unacceptable distortion of the primary electrocardiographic wave form. Reconstruction of the 12 lead electrocardiogram from the vectorcardiogram is probably not valid because coefficients for reconstruction are unique for each individual.[19] Analog and digital storage is extremely dependent upon instrumentation, and scientifically sound guidelines should be followed.

The Canadian colloquium on computer-assisted interpretation of electrocardiograms[20,21] and the American Heart Association Committee on Electrocardiography[8] have outlined state of the art specifications for equipment. The Hollerith cards with 1/2 inch (1.27 cm) analog tape mounted on them can be keypunched with patient information, diagnostic codes and other miscellaneous information[23]; this permits storage of all of a person's electrocardiograms in a series of cards filed together. A special playback unit is required, but all other analog techniques require time-consuming search to identify previous records. Digital storage techniques are desirable and are rapidly becoming available because of technologic advances. Digital storage requires expensive electronic equipment, computer and a computer programs along with unproved compression schemes. Proper techniques for analog to digital conversion are important.[24] However, in conjunction with a computerized registry, a disc pack costing several hundred dollars probably will be able to store up to 100,000 electrocardiograms. Whatever storage medium is used, its limitations should be recognized so that an attempt is not made to do things with the stored data that are technically impossible, such as high frequency electrocardiographic analysis from analog tape data.

Storage of Other Records

The same quality for storage of records as previously indicated for the resting electrocardiogram is necessary for Holter monitoring and exercise test electrocardiographic recordings. When computer techniques are applied to these diagnostic procedures and an interpretation or "compressed" record is generated, it is advisable that these techniques be verified before their results become the only data stored. Signal averaging can lead to distortion,[25,26] and even computer measurements can be in obvious error since they are dependent upon imperfect algorithms. Enough of the actual recording should be made available to justify the diagnostic interpretation of appropriate portions of these tests.

Review and Recommendations on Electrocardiographic Instrumentation

Introduction

Optimal quality of electrocardiographic records cannot be achieved without accurate instrumentation for amplifying, transmitting, storing and displaying the electrocardiogram. The importance of using recorders that meet minimal performance standards has been frequently stressed by those who developed the empiric electrocardiographic diagnostic criteria.[27–29] The American Heart Association has published recommendations for standardization of leads and specifications for instruments in electrocardiography and vectorcardiography for many years.[22,30] More recently, as a result of medical device legislation,[31] the Food and Drug Administration (FDA), by contract with Utah Biomedical Test Laboratory (UBTL),[32] has drafted a performance standard for electrocardiographic devices.[35] In Europe, the International Electrotechnical Commission (IEC) has been formulating a similar standard.[34] Various Canadian groups have been concerned for several years about developing instrumentation standards[20] and evaluation criteria[35] for computer-assisted electrocardiographic processing. An instrumentation subcommittee of the joint advisory committee for the Canadian Cardiovascular Society and the Canadian Heart Foundation has recently published such a paper.[21] There are two de facto commercially used standards in regard to telephone transmission of the 12 lead electrocardiographic signals and patient identification information.[36,37]

Purpose of Standards

The purposes of these standards vary greatly. The FDA and IEC standards are intended to be enforceable standards that impose minimal safety and performance requirements. Their requirements are generally stated as "shall," and test methods for measuring compliance with the standard are carefully defined. The requirements of the American Heart Association and Association for the Advancement of Medical Instrumentation and Canadian standards, developed by voluntary consensus user groups, usually use the word "should" for requirements. They are generally intended only as guidelines and recommendations, and do not have to be met by every electrocardiographic recorder sold on the market. Lastly, there are the manufacturers' design specifications[36,37] for patient identification and 12 lead telephone transmission. These are essential for the designer of automated computer electrocardiographic acquisition and interpretation.

Scope of Electrocardiographic Instrumentation Standards

A brief review of what is covered in the various standards should help to focus attention on problem areas in electrocardiographic instrumentation and to establish a basis of the Task Force II recommendations. Requirements for 12 lead and vectorcardiographic instrumentation in general have been well defined by existing standards.[8,33,34] This is not the case for newer electrocardiographic diagnostic methods such as exercise testing, Holter monitoring and esophageal, endocardial and bundle of His recordings. Requirements for magnetic and paper recorder accuracies for rhythm strip in intensive and coronary care units are covered to a limited extent.[33,38]

The latest American Heart Association recommendations[8] cover the broadest range as regards diagnostic quality electrocardiographs including analog to digital conversion, tape recording of electrocardiograms, amplifier characteristics, auxilliary outputs and lead nomenclature and placement. The lead nomenclature and placement for endocardial and esophageal leads are proposed in detail. However, instrumentation requirements for this type of recording are not defined.[8] The FDA-UBTL standard in its coverage of electrocardiographic monitors encompasses requirements for specialized equipment such as Holter, stress test and rhythm strip recorders, but the detailed record format and accuracy requirement for these applications are not covered by any of the standards. The proposed Canadian standard[21] specifies in great detail electrocardiographic amplifier and telephone transmission characteristics for applications of computer processing. The two industrial standards[36,37] specify lead sequencing and timing, the frequency modulation, multiplexing of three channel signal and the transmission of patient identification information. Recommendations for functional requirements and tentative performance specifications for automated exercise electrocardiographic systems have been drawn up by Rautaharju et al.[39]

Comparison of Instrumentation Requirements

The performance requirements for single channel and multichannel electrocardiographic recorders are comprehensively covered by the American Heart Association, FDA-UBTL and IEC standards.[33,34] Table V summarizes the variables specified in these standards. The FDA-UBTL fourth-draft requirements have been harmonized with the IEC standards to such an extent as to require only one column in the table. The FDA-UBTL standards as well as the American Heart Association standard recommendation contain extensive rationale to justify these requirements.

The American Heart Association requirements are, with only a few exceptions, more exacting than the FDA standard. This is particularly true of the overall accuracy, common mode rejection, drift rate, standardization voltage accuracy and noise. There is little question that most recorders should not only meet the American Heart Association requirements when new, but should be maintained at that performance level when in clinical use. It is realized, however, that a total system amplitude error of less than ±5 percent and the 100 hertz frequency response can be achieved only with careful periodic maintenance and if technicians are trained to recognize abnormal performance in frequency response, trace hysteresis and paper speed.

As mentioned previously, the FDA and IEC standards are minimal enforceable performance standards that should eventually be met by all 12 lead and vectorcardiographic recorders. The FDA standard does not impose requirements on recorders already in clinics and hospitals. This is an area where the recommendation of the American College of Cardiology and the Task Force can play an important role in improving and maintaining high quality electrocardiographic recorders.

Pacemaker recording requirements, as well as ability to withstand defibrillator overloads, are covered in the FDA standard and are not specified by the American Heart Association. It is recommended that the FDA requirements be accepted in these areas.

As regards the safety requirements of patients, isolation and leakage current, the American Heart Association recommendations now exceed those being contemplated by other organizations such as the Association for the Advancement of Medical Instrumentation, Underwriters Laboratory and National Fire Protection Association. The leakage current standard[42] of the Association for the Advancement of Medical Instrumentation is undergoing balloting at the American National Standards Institute to determine whether it should be adopted as a standard approved by the Institute. If such is the result, the FDA is most likely going to adopt it as an FDA baseline standard. The problem with accepting the more exacting American Heart Association recommendations is that several of the leakage currents, that from chassis to ground and that resulting when 120 volts are applied to the leads, cannot be met by many manufacturers without redesign and certainly not by older equipment still in use in hospitals.[32]

Computer Communications and Electrocardiographic Transmission

Several standards are in use or have been proposed in the area of transmission of electrocardiographic signals over telephone lines and telecommunications facilities.[8,21,36,37,41]

TABLE V

Functional Performance Requirements of the Food and Drug Administration (FDA) and American Heart Association (AHA) for Direct Writing Electrocardiographs

Requirement Description	Minimal or Maximal	Units	Minimal or Maximal Value of Performance Variables	
			FDA Type I	AHA
Range of linear operations of input signal	Minimal	mv	±5	±7
Skew rate range	Minimal	mv/sec	320	400
Direct current offset voltage range	Minimal	mv	±300.0	±200
Allowed variation of amplitude with direct current offset	Maximal	%	±5	±5
Gain control chart recorder	Minimal	mm/mv	10 and 5	20,10,5
Gain drift rate				
After first minute	Maximal	%/min	±0.33	NS
Total drift in 1 hour	Maximal	%	±5	±2
Speed selection	Minimal	mm/sec	25 and 50	25 and 50
Speed error				
For 0.20 to 2 second recording	Maximal	%	±5	±5
Recordings greater than 5 seconds	Maximal	%	NS	±2
Width of display	Minimal	cm	4	5
Divisions on preruled paper	Minimal	div/cm	10	10
Error of rulings	Maximal	%	±2	±2
Trace width	Maximal	mm	1	1
Reading visibility	Minimal	mm/sec	1600	2000
Time marker error	Maximal	%	±5	±2
Allowable error for ±5 mv signals	Maximal	%	±10	±5
	or			
	Maximal	μv	50	25
Upper cutoff frequency (3 DB)	Minimal	Hz	100	100
Allowable overshoot to step response	Maximal	μv	100	NS
Decay time constant after step input	Minimal	sec	3	3.2
Error in electrode weighing factors	Maximal	%	5–10	±7
Hysteresis	Maximal	μv	50	20
Standardization nominal value	. . .	mv	1.0	1.0
Allowable deviation from value obtained with 1 mv at leads	Maximal	%	±5	±2
Input impedance any lead at 10 Hz—variable with frequency	Minimal	MΩ	2.5	2.5
Direct current any lead	Maximal	μA	0.1	1.0
Common mode rejection-allowable noise				
With 28 v, 60 Hz and ±300 mv DC and 5 kΩ imbalance	Maximal	μA	100	NS
With 336 v, 60 Hz applied through 22 pF capacitor and 100 kΩ imbalance	Maximal	μv	NS	2000
Noise internal RTI—p-p	Maximal	v	40	28
Multichannel cross talk	Maximal	%	2	1
After reset by automatic or manual means, return time to within linear recording range	Maximal	sec	3	NS
To within 1 mm of center	Maximal	sec	NS	0.5
To within 3 mm of baseline after lead switching	Maximal	sec	1	NS
Baseline drift rate RTI	Maximal	μv/sec	10	NS
Total drift RTI	Maximal	μv in min	500 in 2	50 in 50
No damage differential voltage 60 Hz				
Applied for 10 seconds	Minimal	v p-p	1.0	NS
Applied for 5 seconds through 100 pF capacitor	Minimal	v p-p	NS	336
Defibrillator protection			Yes	Yes
Overvoltage (applied to 100 ohm load and electrodes)	Maximal	v	5000	336
Energy (applied to 100 ohm load and electrodes)	Maximal	J	400	NS
Pacemaker display capability pulse	Maximal	mv	500	NS
Duration		msec	1	NS
Leakage current for isolated leads	Maximal	μA	20	10
Chassis	Maximal	μA	100	10
With 120 v applied to electrodes	Maximal	μA	20	6

NS = not significant; RTI = electrocardiographic amplifier input.

TABLE VI

Instrumentation Standards for Electrocardiographic Transmission and Computer Acquisition

Variables	Units	Canadian[21] 1976	AHA[8] 1975	Commercial Type 1[37]	Commercial Type 2[36]	Emergency Telemetry[41]
Dynamic range						
Maximal signal	mv	±5	±7	±5.0	±5	±5
Minimal DC offset	mv	ns	±200	±200	±400	ns
Frequency response						
Upper 3 db	Hz	125	100	100	100	40
Lower 3 db	Hz	0.05	—05	dc	dc	0.01
FM transmission						
FM carrier ch 1	Hz	1075	1075	1075	1075	1400
FM carrier ch 2	Hz	1935	1935	1935	1935	na
FM carrier ch 3	Hz	2365	2365	2365	2364	na
Sensitivity	Hz/mv	50,25	ns	50,25	−40,−20	30 to 50
Maximal signal	mv	±2.5,±5	ns	2.5,±5	±2.5,±5	±50
Patient identification code		TT	TT	TT	ASCII	Voice
Allowable error (1 mv)	%	±3	±5	±5	±2	ns
Allowable noise rms	μv	<5	<10	<5	<20	<10
Computer sampling						
Resolution ECG	μv	10	10	1.25	5	na
Resolution A/D	bits	10	10	12	10	na
Minimal sampling rate (samples/sec)		500	500	250	250	na
Maximal skew between channels	μsec	100	1000	1300*	2000‡	na

A/D = analog to digital; AHA = American Heart Association; ch = channel; DC = direct current; ECG = electrocardiogram; FM = frequency modulation; na = not applicable; ns = not specified; rms = samples/sec; TT = touch tone.
* Skew due to the A/D conversion process only.
‡ Total recording system skew.

All of the proposed standards, except for emergency telecommunications,[41] are concerned with transmitting three channel electrocardiographic signals of full diagnostic quality.

Table VI is a summary of proposed design standards. Note that there is substantial agreement in terms of dynamic range, frequency response and frequency modulation characteristics. The center frequencies for the three channel electrocardiographic transmission—1,075, 1,935 and 2,365—are standardized bases on the Bell 604 data sets. The allowed deviation of frequency around these center frequencies varies considerably in that the Canadians recommend no more than ±125 hertz (Hz); one commercial type no more than ±100 Hz; and the other ±125, but allows ±175 Hz to extend the dynamic range. Note that in all cases except for emergency transmission, the standard gain of 1,000 can be used only for up to a signal of ±2.5 mv. This corresponds to a ±2.5 cm deflection of the chart recorder at a gain of ±10 mm/mv. An incompatibility in frequency modulation gain exists between the type 2 commercial system (−40 Hz/mv) and that used by others (+50 Hz/mv). This incompatibility is extended in that the Canadian and the commercial type 1 standards use the touch tone coding for transmitting lead identification and patient information, while the commercial type 2 transmits frequency-modulated ASCII code at 110 band rate. The ASCII system had the advantage of direct compatibility with many computer languages using ASCII code, the flexibility of both alphabetic and numeric transmission and ability to sense errors by using a parity bit transmission. The touch tone system is simpler and more compatible with the standard telephone lines. The disadvantage of having two systems is that electrocardiographic transmission cart and computer interface hardware and input and output software cannot easily be made compatible. It is in the public interest if the users of telephone transmission are not restricted in their options of computer use by incompatible services of two systems.

The Task Force concurs with the recommendation of the American Heart Association and the Canadian group of sampling each channel at 500 samples/sec, in particular where data bases for empiric diagnostic criteria are being collected. The Task Force realized that most electrocardiographic computer analysis programs use the 250 sample/sec rate,[10] and this is acceptable where the makeup and diagnostic accuracy of the program justify it.

It is of paramount importance that the total recording, transmission and sampling system be such as to preserve the fidelity of the expected range of electrocardiographic signals. At a minimum, this means that the dynamic range of the total system be as good as that of the direct writer. Any signal recorded on the chart paper should be capable of being modulated and demodulated with minimal distortion in time and amplitude and without amplitude clipping. The analog to digital converter input voltage range should coincide with or exceed the voltage range produced by the demodulator. Finally, electrocardiographic signals in the range between +5 and −5 mv should be capable of being reproduced at the end of the transmission system with no visible difference from that recorded directly from the patient.

Instrumentation for exercise testing includes both a monitor scope and a direct writer. Since S-T segment change is the main variable to be measured, fidelity of the signal recording, particularly in the low frequency range, is essential. It has been suggested that exercise testing instruments conform to the fidelity recommendations of the American Heart Association for 12 lead electrocardiographs and vectorcardiographs.[39] This Task Force agrees with this recommendation and urges that unless justified by the need of experiment, a frequency response range of 0.05 to 100 hertz or greater be used for exercise testing.

Legal Implications

Objectives

The ultimate objective of a legal system, as it applies to medicine, is to prevent harm to the patient. The legal system includes (1) an appraisal to determine whether or not injury has been sustained, (2) a determination of whether or not the injury has been caused by failure of a legally applied standard of care, and (3) legal redress to ameliorate unnecessarily sustained injury. Moral and ethical awareness, together with the recognition of the potential use of the legal apparatus, provides the incentive for a medical system to know and abide by its legal responsibilities.

The two main areas of potential liability associated with an electrocardiographic system are civil (for malpractice or negligence) and criminal (for unauthorized practice of medicine).

Sources of Liability

Any one of the several components of an electrocardiographic system may cause data to be erroneous or lacking, or to be interpreted incorrectly, thus causing the generation of an incorrect diagnosis. Certain components may cause the system to be unsafe. Thus the participants of an electrocardiographic system must be alert to civil or criminal liability.

An electrocardiographic system may include: (1) patient electrodes; (2) technicians; (3) the recorder; (4) the electrocardiographer; (5) generation, reproduction and distribution of the electrocardiogram and its report; (6) storage of the electrocardiogram and its report; (7) telephonic or radio wave transmission of the electrocardiogram; (8) computer analysis of the electrocardiogram; (9) short-term electronic and longer-term magnetic storage of the electrocardiogram and its report; (10) magnetic accumulation of many hours of electrocardiographic data (Holter monitor recording or a compressed data system); (11) a rapid scanner; (12) electrocardiographic monitoring equipment; (13) an arrhythmia alarm system; (14) computer arrhythmia analysis; (15) trend analysis and trend plot generators; (16) exercise stress testing equipment; and (17) fetal electrocardiographic monitors among others. Thus, even in its simplest form, an electrocardiographic system is complicated, and an enormous effort may be required to ensure that such a system operates within the law, that is, that (1) there is no unauthorized practice of medicine, (2) safety standards set by law are followed, (3) the standards of quality set by law are met, and (4) quality control of the electrocardiographic system and its products prevents negligence, including malpractice.

Many safety and quality standards are included in the most recent FDA draft on minimal performance standards for electrocardiographic recording devices. Legislation allowing the FDA to set such standards has already been passed. Thus, these standards will have the force of law. However, the FDA standards may not cover some components of electrocardiographic systems, such as patient electrodes, technician competence, quality of telephonic or radio wave transmission, quality of computer analysis, quality of electronic and magnetic storage, quality of electrocardiographer interpretation, quality and efficiency of reproduction and distribution systems. Some established, some untested and certain theoretical legal implications exist for substandard quality of some of these components.

Liability for Electrocardiographic Interpretations

Cardiologists have been sued for incorrect or inappropriate electrocardiographic interpretations. However, the question has never been answered as to whether the remote cardiologist, by virtue of the analysis of the electrocardiogram, is practicing medicine. "[One does not hold himself] out to the public as being engaged in the diagnosis or treatment of ailments of human beings . . unless assertive conduct is directed toward the public with a view to establishing a physician-patient relationship."[42] Furthermore, this principle is more strongly stated in a Maryland case. Maryland apparently specifically exempts from the unauthorized practice statute consultations by an out of state physician with an in-state licensed practitioner.[43]

Computer programs: Institutions have been brought into court because of an erroneous computer analysis of an electrocardiogram. However, the Department of Registration and Education of Illinois has indicated that an institution is not practicing medicine by providing computer analysis of electrocardiograms for physicians. If a court test were to uphold such an opinion, then an institution providing such a service might be held only to negligence standards, or possibly to malpractice standards, but would be under no criminal liability for unauthorized practice of medicine.

The need for, and the importance of, computer application to medical and hospital practice is increasingly recognized by the legal community.[44] Computer programs for electrocardiographic analysis have improved greatly over the last several years, so that wave form recognition and implementation of recent criteria for electrocardiographic abnormalities are of reasonably high quality. These programs also perform some quality control analyses such as tests for frequency response, differentiation among various types of artifact including 60 cycle interference, muscle tremor, telephone line noise and limb lead placement errors. This type of quality control may not be included in the final draft of the recent FDA standards, but such standards may follow in the future and, like the recent ones, may carry the force of law. These standards and those that might be related to storage and retrieval should be developed by groups (including institutions and commercial enterprises) that have had the most experience in this area. Certain limited standards for transmission and processing of electrocardiographic data have already been suggested by the American Heart Association. Institutions are civilly responsible for the quality of these automatic electrocardiographic systems whether or not such a system consists of the practice of medicine, in the same way that an unlicensed practitioner is required to exercise the same professional standards of skill and care that prevail among licensed practitioners.[45] Thus, quality control is the best protection against civil liability because the question of whether the

practice of medicine is involved may not even be pertinent. "The mere want of a license does not raise any inference of negligence and if an unlicensed practitioner exercises the requisite skill and care in administering treatment to a patient he is not liable in damages from injury to the patient from such treatments, merely because of this want of license."[45]

Criteria for diagnosis and competence: One of the most difficult questions is whether or not there are legal ramifications related to criteria for diagnosis and recognition of competence to read electrocardiograms. Certain obvious abnormalities should be recognized and similarly interpreted by all physicians who read tracings, as well as by all computer analysis programs, and this expectation is most likely to be upheld by the courts. It would seem to be proper for this Task Force on quality of the electrocardiogram to urge that certain obvious criteria generate the appropriate diagnosis because of the probable legal obligation to do so. However, a great many criteria, perhaps most, are in a state of flux. Suggesting that standardization of criteria is equivalent to high quality interpretation may be incorrect and may inhibit further development of good criteria. It should be understood that although publication of a single set of "recognized" electrocardiographic criteria would be useful to many physicians these criteria might become the standard upon which the courts would rely. The use of newly developed criteria, such as those that might be available from the huge data banks of electrocardiographic computer analysis systems, would be discouraged because of inevitable delay involved in changing the single published set of recognized criteria.

The problem of evaluating the electrocardiographic reader is in some ways similar to the problem of evaluating the criteria, because the reader and the tester must depend upon these criteria. The difficulty lies in the state of flux of many diagnostic criteria.

An additional problem involves patients' right to privacy. The patient data transmitted to an electrocardiographic laboratory, especially a distant one, must be used with discretion to avoid invasion of privacy.

Legal Aspects: Summary and Recommendations

This Task Force therefore makes the following points and recommendations:

1. We point out that minimal standards for certain components of electrocardiographic systems have been developed by the FDA and will carry the force of law.

2. Additional standards for some of the remaining components of electrocardiographic systems will probably follow, and possibly will carry the force of law. These should be developed by cooperation among medical centers, commercial enterprises and other institutions that have had the most experience in the areas in question.

3. We urge that computer analysis of electrocardiograms not be considered the practice of medicine, whether distribution of the analysis is within the state or into another state, so that physicians are not unduly restricted from receiving such service, nor institutions with computer resources restricted from providing it. However, it is premature to propose that any computer electrocardiographic service is so well accepted that its availability is mandatory in the absence of a competent local electrocardiographer.

4. Similarly, we urge that, although the interpretation of a tracing by a physician electrocardiographer in one state *might* be considered the practice of medicine in that state, the distribution of that interpretation to a second state not be considered the practice of medicine in the second state.

5. We suggest that standardization of certain criteria may improve the quality of electrocardiographic systems; however, before a compendium of electrocardiographic criteria is developed, the effects of the legal implications upon the users of criteria subsequently formulated should be considered.

6. We point out that patient data transmitted to an electrocardiographic laboratory increase the reliability of the interpretation, but that such data are private and must be used with discretion so as not to violate the right to privacy of the patients involved.

APPENDIX I

Technical Tracing Quality Criteria*

1. Baseline quality. The minimal slope of the baseline in any electrocardiographic sample will be reported as follows:
   - 4 = 0 − <0.1 mv/sec (1 mm in 25 mm at slow speed)
   - 3 = 0.1 − <0.4 mv/sec
   - 2 = 0.4 − <1.0 mv/sec
   - 1 = 1.0 mv/sec but has at least 3 QRS complexes in a straight line
   - 0 = not having any 3 consecutive QRS complexes in a straight line
2. Powerline artifact, 50 or 60 hertz. This will be measured from peak to peak where the artifact is the most obvious:
   - 4 = no visible artifact
   - 3 = 0 − <0.1 mv artifact
   - 2 = 0.1 − <0.2 mv artifact
   - 1 = 0.2 − <0.3 mv artifact
   - 0 = ≥0.3 mv artifact
3. Muscle tremor artifact and intermediate frequency artifact ("baseline jiggle"). This will be measured from peak to peak in the highest quality part of any individual lead group sample:
   - 4 = no visible artifact
   - 3 = 0 − <0.1 mv artifact
   - 2 = 0.1 <0.2 mv artifact
   - 1 = 0.2 − <0.3 mv artifact
   - 0 = ≥0.3 mv artifact
4. Clipping or lost electrode. This evaluation is performed on the portion of the tracing having best technical quality:
   - 4 = no clipping or lost electrode
   - 2 = clipping which does not involve the ST-T waves
   - 0 = clipping which does involve the ST-T waves or 0 represents also a lost electrode in that lead group
5. Limb lead reversal. This evaluation is performed on the worst example of the tracing, that is, if it occurs any point in the electrocardiographic set the coding is performed.
   - 4 = no limb lead reversal anywhere in the test
   - 0 = limb lead reversal occurring somewhere in the test

* These criteria, employed by the Lipid Research Clinics Project (LRCP) Central Electrocardiographic Laboratory, are recommended for general use, and a "Class I" record is considered satisfactory for unrestricted interpretation. This is defined as a mean score of 3.00 or more using the scoring schedule found in the LRCP Mini-Memo 4(10), September 1976.

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Task Force III: Computers in Diagnostic Electrocardiography

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This Task Force was commissioned to examine the role of computers in optimal electrocardiography. The broad terms of reference assigned to the Task Force cover various aspects of computer applications in clinical electrocardiography with specific objectives to examine the present state of the art of computer-aided interpretation of electrocardiograms and to identify optimal features in programs and processing systems.

Some consideration was initially given to documenting comparative performance data on computer electrocardiographic programs on the basis of already published evaluations. After considerable deliberation, the consensus of the Task Force was that the methodology for computer program evaluation has to be first clearly delineated and specified before various programs can be compared. Furthermore, the majority of the Task Force favored comparative program evaluation using well defined test libraries, with appropriate clinical documentation and specific selection criteria for each test group. It was believed that documentation of actual comparative program evaluation results should be delayed until the evaluation methods are defined and until protocols and case selection criteria are agreed upon. Progress in these aspects is reported by Task Force IA of this Conference on Development of a Data Base for Electrocardiographic Use. This Task Force on Computers thus assigned a high priority to efforts to specify methodology of electrocardiographic program evaluation.

Excluded from the scope of this report are applications of computers in interpretation of exercise electrocardiograms, monitoring of critically ill patients, ambulatory monitoring and associated arrhythmia analysis, interpretation of fetal electrocardiograms and use in epidemiologic studies. Several monographs and reviews have been published on computer analysis of electrocardiograms.[1–26] The reader is advised to consult particularly References 1, 3 and 6.

Description of Computer Electrocardiographic Processing Systems

General Overview

Computer systems for the analysis of electrocardiograms have as their main component a program that performs measurements, interprets the clinical significance of the measurements and possibly compares the interpretation and measurements with those derived from the patient's previous tracings. These computer systems usually perform additional functions, such as storing the electrocardiograms for future reference. The electrocardiographer may use the systems for writing his reports by simply editing the computer interpretations. One key feature of an electrocardiographic processing system is that the reviewing physician, as well as the recording technician, can have access to it from almost any telephone set.

Computer Electrocardiographic Programs

A program may have four basic components:

1. *A measurement program,* which extracts from the electrocardiogram a set of measurements. This is further subdivided into an automatic wave form recognition section and a measurement section, which then extracts from the wave forms, a set of values and contours for interpretation.
2. *An interpretation program,* which generates the final statements to be reported by the program.
3. *A rhythm program,* for identification of the cardiac rhythm.
4. *A comparative analysis program,* which compares serial electrocardiograms and notes significant changes between successive tracings.

Statements of interpretation: Detailed descriptions of the characteristics of these components and the differences between various program designs are covered in Appendix I. The key feature of the programs with respect to their clinical utility is the set of statements used for reporting the interpretation. According to the way in which optimal disease or condition-related electrocardiographic criteria can be established and evaluated, one may distinguish three types of statements (Table I).

1. *Type A statements* define a degree of likelihood for the presence of a specific disease or clinical condition. Their accuracy can be determined on a statistical basis using information independent of the electrocardiogram.
2. *Type B statements* identify electrophysiologic conditions defined and detected primarily by the electrocardiogram itself. In some instances the condition can be confirmed by invasive electric probes. Thus, the accuracy of type B statements is determined by the quality of the program's wave recognition and measurement modules.
3. *Type C statements* describe features in the electrocardiogram that may or may not be related to anatomic lesions or the physiologic state. Although they may have importance in the context of other clinical information, taken by themselves their specificity is low or unknown (for example, nonspecific ST-T changes).

TABLE I

Three Categories of Electrocardiographic Statements Amenable to Different Types of Evaluation

I. Documentable by nonelectrocardiographic means
Infarction/injury
Hypertrophy/enlargement/overload
Pulmonary disease
Metabolic/digitalis effect
Ischemia (possibly documentable)
II. Detectable primarily by electrocardiography
Rhythm disturbances
Atrioventricular blocks
Pacemaker rhythms
Pacemaker artifacts
Bundle branch blocks
Fascicular blocks
Preexcitation (Wolff-Parkinson-White)
III. Purely morphologic descriptors
Axis deviations
Low QRS voltage
Increased QRS voltage
Nonspecific ST-T abnormalities
Strain
Large T waves

TABLE II

Utilization of Computer Electrocardiographic Programs in 1976[18]

	Annual Volume*	Key References†
Proprietary Programs		
IBM	1,400,000	1, 3, 12
TELEMED	1,400,000	3
Mayo	325,000	1, 3
Cro-Med	500,000	3, 13
Hewlett-Packard	600,000	3
Phone-A-Gram	140,000	. . .
Siemens	150,000	3
Public Domain		
ECAN	195,000	1, 14
VA	160,000	1, 3, 15
CEIS	110,000	. . .
LDS	18,000	16
Glasgow	12,000	1, 3, 17
Hannover	18,000	1, 3
CIMHUB	22,000	3

* Annual volume is given for programs for which the reported volume exceeds 10,000 electrocardiograms.

† See list of references at end of text. Several other programs are described in references 1 and 3, including the TNO modular program of van Bemmel et al. and the Lyon program of Arnauld and Rubel.

Other Systems Features

Although the accuracy and reliability of the computer electrocardiographic program are important characteristics of an interpretation system, the program's utility in a clinical environment is significantly influenced by several other factors: (a) the method of electrocardiographic transmission and entry into the system; (b) permanent storage of electrocardiograms; (c) format and style of the report; (d) the method of physician review and generation of the final report; (e) other management aids such as quality data on technicians' performance, equipment quality control, etc.; and (f) flexibility for system modifications. A detailed description and critical reviews of features of available systems are presented in Appendix II. The identification of optimal features of a system is dependent on the particular environment in which the system operates. This fact will have an important effect on the comparative evaluation of systems.

The system features discussed in this section involve to some extent subjective criteria, which make the results "soft" but by no means useless. Comparative results can be obtained even by these categories if standardized methods of evaluation are used (for details see Appendix III).

Present State of Computer Interpretation of Electrocardiograms

Level of Utilization

On the basis of the Arthur D. Little report,[2] it can be estimated that in 1976 about 10 percent of the electrocardiograms recorded in hospitals and less than 2 percent of those taken in physicians' offices were processed by computer. Table II indicates the reported utilization in 1976 of electrocardiographic programs developed in private and public sectors. Growth indicators suggest that we are at the beginning of a period of rapid expansion of interpretation by computer. It was not always possible to verify the utilization figures at the source for the data given in Table II. Reservations are expressed about growth patterns predicted in various industrial forecast reports.

Analysis of the patterns of diffusion of computer-aided electrocardiographic interpretation into patient care suggests that the initial level of user acceptance is determined by a variety of factors in addition to the actual diagnostic accuracy of the program. Although diagnostic accuracy plays the main role, efficiency and convenience of physicians' review procedures, measurement reliability, reporting style and format and customer support may significantly influence the acceptance of any given electrocardiographic program or processing system. The history of many early failures and a few recent successes indicates that under rigorous automatic quality control, and by providing the physician-reviewer with a convenient, efficient schema for error detection and correction, the total electrocardiographic processing system can function despite deficiencies in the computer measurement and interpretation program.

Advantages of Computer-Assisted Electrocardiographic Interpretation

Electrocardiographic processing by a computer (Table II) offers several advantages. Some of the advantages should be considered primarily subjective impressions rather than documented facts because of the lack of objective systematic comparative analyses of the relative merits of manual and automated processing. There is a need for additional systematic evaluation, particularly regarding cost comparisons.[2]

Computer-aided electrocardiographic processing *enhances the capacity* of handling high volumes of

electrocardiograms. This benefit is particularly evident in large hospitals or groups of hospitals that have pooled their services. Although cost reduction through automation or semiautomation of electrocardiographic processing has not been clearly demonstrated or achieved on a large scale, it is reasonable to expect that *cost containment* can be achieved by increasing the capacity of the system to handle an increasing electrocardiographic volume without a proportionate increase in medical personnel and space required for the service.

The benefit of *improved turnaround* and *distribution* of the service is particularly important to small hospitals[2] and physicians' offices. Rigorous *quality control,* particularly in a real time electrocardiographic processing system, can substantially enhance record quality and thus the reliability of interpretation. Recent advances in mass storage technology result in substantial improvement in the *efficiency of record storage and retrieval.* This will greatly facilitate implementation of comparative electrocardiographic programs.

Computer-aided electrocardiographic interpretation may improve the quality of interpretation service by providing a *uniform standard of* interpretation for the group of physicians in charge of reviewing computer interpretations.

Computer analysis of electrocardiograms has had a substantial impact on *basic research in electrocardiography,* and has increased the feasibility of and capacity to carry out heart disease prevention programs and cardiovascular epidemiologic studies.

Since the objective of computer electrocardiography is to improve the quality and delivery of patient care, the users most likely to benefit from the *availability* of computer-aided electrocardiographic interpretation service are physicians' offices and hospitals with few cardiology consultants.

The impact of computer-aided interpretation may be particularly important for *emergency electrocardiographic services* in situations where a cardiologist is not continuously available. Increased coverage can thus be provided, with improved availability of electrocardiographic reports and physician review or cardiologic consultation, or both.

The introduction of computer-aided interpretation in larger regional hospitals with an adequate cardiology staff may be less pressing and beneficial than elsewhere. The utility and acceptance of computer-aided electrocardiographic interpretation may largely depend on the objectives and priorities of the cardiology department and the professional qualifications of the cardiology staff. Improved *efficiency* of electrocardiographic reporting regarding the time spent by the professional and clerical staff may become the key determinant leading to the decision to implement computer-aided processing systems in larger hospitals to meet the increased work load.

Problem Areas and Disadvantages of Electrocardiographic Interpretation by Computer

As with any other laboratory test or diagnostic procedure, computer analysis of electrocardiograms can be abused. Relevant medical-legal and economic issues are discussed in the reports of other Task Forces of this conference. The following possible disadvantages are of particular concern.

Increasing uncritical reliance on computer interpretation: This may result in deterioration in the quality of teaching electrocardiography. On the other hand, with appropriate planning and use, a semiautomated interpretation system should become an efficient and reliable teaching tool because many electrocardiographic interpretation programs provide with the report the exact criteria for the given interpretation. Equally important for efficient teaching is easy access to already validated reports. Electrocardiographic test libraries, which provide additional electrocardiogram-independent clinical information, should add another dimension for in-depth learning of computer-aided interpretation.

Easy availability of electrocardiographic interpretation: This can possibly lead to an unwarranted increase in utilization of the service. Although an improvement in the availability of the service may initially lead to an increase in volume of electrocardiograms, this increase soon levels off.[2] The increase may reflect correction of underutilization that existed before a computer-based service was introduced.

Mass applications of computer interpretations: With easy and increasing availability of computer-aided electrocardiographic interpretation, there is considerable pressure to provide large-scale interpretation service in mass applications, such as periodic health check-ups, clearance for physical fitness programs, screening of selected populations at the community level or groups of employees in industry and screening of life insurance applicants. These areas require study when one judges the utility of computer processing of electrocardiograms in terms of costs and benefits and the potential impact on the ultimate consumer, the patient. Perhaps the crucial question to be answered by those who advocate mass application of computer-aided interpretation is, "which electrocardiographic findings should be reported?" And perhaps the most prudent answer is that only those findings should be reported that are sufficiently important for medical management of the person concerned, or that have adequately proved significant predictive value in conditions in which an appropriate medical intervention can retard or stop the progression of the underlying disease.

Lack of independent objective standard: The key problem in the assessment of the present state of the art of computer electrocardiographic interpretation is the lack of an independent objective standard in most past evaluation attempts. Pipberger and Cornfield[8] noted that most of the published evaluations are inadequate and often misleading because they have not tested diagnostic accuracy against electrocardiogram-independent evidence: "Investigations which lack an objective reference standard will never provide us with an answer. In the interest of better patient care, answers need to be obtained soon." [8]

Inadequate standardization of definitions and measurement rules: Computer programs, although by

no means immune to noise and artifacts, have produced a significant improvement in the consistency of measurement and interpretation in comparison with visual procedures. The consistency of measurement is of particular importance in comparing serial tracings. The magnitude of this problem in electrocardiographic classification was pointed out by Prineas and Blackburn,[9] who observed that more than one of four cases of reported events (significant "worsening") coded as new infarctions was due to visual coding inconsistencies in spite of triplicate reading and arbitration of disagreements. Measurement and interpretation of the same set of electrocardiograms by *different* computer programs will produce a considerable number of disagreements. The primary source for these differences is inadequate standardization of definitions and measurement rules. It should be recognized that current visual measurement rules[10] are inappropriate for direct implementation in a computer program.

Classification and coding schemes: Several groups of electrocardiographers have proposed electrocardiographic criteria or coding schemes that have been or could be considered for computer implementation. From these classification schemes the Minnesota Code[11] has been widely used in epidemiologic studies. A severe limitation in the clinical use of these codes is the lack of separation between diagnostic classification criteria and criteria for classification of purely descriptive morphologic electrocardiographic features. This problem will be further considered in Appendix III.

Future electrocardiographic classification schemes and program development efforts are likely to rely heavily on clinically well documented data banks for both development and testing. Several such data banks are now being developed. The effort involved in these undertakings can be substantial, especially in the collection and documentation of data banks for serial comparison programs.

Computer analysis of pediatric electrocardiograms: This subject has until recently received a low priority among program designers and users. Special problems exist in this area because of considerable differences in signal characteristics in comparison with adult electrocardiograms and because of the fast, profound evolution of electrocardiographic patterns from birth to adolescence. In view of the age-dependent "normal" standards in infants and children and the concomitant difficulties in differential diagnosis between normal and abnormal conditions, it is reasonable to expect that computer analysis should significantly facilitate the interpretation of pediatric electrocardiograms. Systematic cooperative research and development efforts in this field should be encouraged by the establishment of suitable clinical data bases for program development and testing.

Relative merits and deficiencies of existing programs: Past reports on acceptance by and experience of users of computer programs have focused mainly on systems that have been successful. The Task Force recognizes the bias possibly introduced by this factor in this and other reports and suggests that future evaluative reports on the state of the art of computer-aided electrocardiographic interpretation pay more attention to the opinions of important sectors of "nonusers" and the experience of former users of programs and systems that have not been successful.

This report is deficient and incomplete in several aspects. Although desirable and optimal features of electrocardiographic programs and processing systems are discussed in general terms and guidelines provided for program evaluation, no attempt is made actually to identify and compare the relative merits and deficiencies of existing programs and systems. Continuing long-term efforts on comparative program evaluation need to be made by parties as free as possible from conflict of interest.

Evaluation Methodology

Accuracy, acceptability, utility and reproducibility: Evaluation procedures must take into consideration the user's specific environment; this will determine the importance of the various system features. A complete method for evaluating computer electrocardiographic programs and systems involves four different aspects: accuracy, acceptability, utility and reproducibility. *Accuracy* is defined as the sensitivity and specificity for type A statements; it is evaluated by using a library of cases for which the diagnosis is determined or excluded by nonelectrocardiographic means. Certain interpretive statements (type B and some type C) can only be evaluated against the standard of a given set of electrocardiographic measurements or criteria established prior to evaluation. *Acceptability* of any electrocardiographic interpretive statement is determined by the reviewing physician and is the only method for evaluation of statements (type C) for which the above methods cannot be applied. *Utility* involves the evaluation of convenience, time-saving, cost-saving and usefulness of the system. *Reproducibility* is a test of a system's stability in the presence of noise, such as powerline interference and patient artifacts. The method for evaluating each of these four aspects is given in detail in Appendix III.

Conclusions and Recommendations.

1. Computerized electrocardiography is being effectively utilized today in many medical institutions. The electrocardiographic analysis programs and the related computer technology in general are still undergoing rapid evolution to meet the specific, widely varying needs and requirements for electrocardiographic processing in any given clinical environment. Growth indicators suggest the beginning of a period of rapid expansion of electrocardiographic processing by computers, resulting in substantial changes in the practice of electrocardiography. During this rapid evolution, all those involved in health care delivery should carefully monitor the medical, educational and economic implications of utilizing this new technology.

Some factors to be evaluated are: (1) verification of the improvement in the quality of electrocardiographic reading when an electrocardiographer uses a supplementary computer interpretation; (2) the impact of electrocardiographic reading quality on the use of

computer service in areas without an electrocardiographer; and (3) the need for new professional education programs to train electrocardiographers to make efficient use of computer-aided interpretation.

2. Electrocardiographic interpretation by a computer is a laboratory test that may lead to a medical diagnosis, once reviewed by a qualified physician.

Diagnostic electrocardiographic interpretation by a computer or a physician reviewer should be subjected to the same kind of rigorous evaluation as any other laboratory test or diagnostic procedure.

3. Lack of an objective reference standard in the majority of past reports on the performance of electrocardiographic programs inhibits analysis of relative merits and shortcomings of various programs. The Task Force strongly supports cooperative efforts for the establishment of test libraries for electrocardiographic program evaluation.

It is recommended that the performance of various electrocardiographic programs be established using such test libraries and evaluation procedures specified in this report. Detailed test results of program evaluation should be made available to program users. The test and development library should be administered by a party free of conflict of interest. In the interim before the test libraries are available, developers of computer programs should provide documentation of the diagnostic criteria used and evidence to support their rationale.

4. Implementation of electrocardiographic analysis programs on computer systems or operating environments that are different from those for which the program was originally designed may significantly alter the program's performance. Considerable problems exist in verifying that a "transported" program is a reasonably close reproduction of the authentic source.

It is recommended that comprehensive test methods be developed to verify that translated or transported electrocardiographic programs perform in all functional aspects identically to the original version. It is further recommended that translators provide accumulation of their efforts to verify the accuracy of their translations.

5. Substantial differences exist between electrocardiographic programs regarding measurement definitions and classification terminology. While recognizing the importance of diversity for innovation, the Task Force considers the lack of standardization of terminology and definitions a substantial impediment to progress. It is recognized that the currently used visual measurement rules and definitions of electrocardiographic "waves" and intervals are too ambiguous to permit a reasonably uniform implementation in computer programs.

Systematic efforts aimed at more consistent and precise electrocardiographic measurement rules, definitions and terminology are strongly encouraged.

6. The scope of the present report excludes several important areas of electrocardiology, that is, exercise electrocardiograms, monitoring and associated arrhythmia analysis, interpretation of fetal electrocardiograms and applications of computers in epidemiologic studies.

In view of the rapidly growing application of computers in these areas, it is recommended that the American College of Cardiology or some other appropriate organization establish task forces to evaluate critically the current state of the art.

APPENDIX I

ELECTROCARDIOGRAPHIC PROGRAM DESCRIPTION

There now exists throughout the world a large number of computer programs that have been specifically designed to analyze electrocardiograms and report the clinical interpretations. In comparing these programs, it is evident that although there are many concepts common to all of the programs, each differs from the others in many ways. Differences are found in both the technique of electrocardiographic classification and measurement of wave forms. The programs generally perform four basic functions, which are independent of each other. Comparison of programs therefore requires comparison of each of the functions separately, namely, measurement, interpretation, rhythm and serial comparison.

Differences in the design of each of these four functions contribute to the reliability and accuracy of a particular electrocardiographic program. To present the state of the art of existing programs, this section outlines some of the differences in the available clinical programs.

Electrocardiographic Measurement Programs

Lead systems: The most notable difference in the programs is the choice of lead systems used for the analysis. Programs use either the standard 12 lead system or an orthogonal X, Y, Z system. The developers of 12 lead programs have primarily restricted their classification strategies to criteria that could be implemented in either an automated or manual system. Thus, most measurements made by 12 lead programs correspond to those that can be used manually by a cardiologist in reading electrocardiograms. Developers of three lead programs, however, have frequently used measurements other than those required for manual reading. Such measurements might include areas, slopes and curvatures.

Location of fiducial measurement points: Single versus multiple channel transmission: The main task in the measurement program is the location of these fiducial points (for example, the onset and the end of the QRS complex). Strategies for location of these fiducial points depend upon transmission to the computer either of simultaneously recorded multiple leads or of a single lead. Location of fiducial points with simultaneously recorded leads is in general easier and produces greater measurement reliability. The extent of improved measurement reliability with simultaneously recorded leads is not precisely known. Therefore, some developers have continued to use single channel transmission systems because single channel computer electrocardiographic carts cost less. Multiple lead transmission, however, is used in both 3 lead and 12 lead analysis programs. With 12 lead systems, the leads are transmitted in four sets of 3 leads each. In searching for the fiducial points on simultaneously recorded leads, the most common technique is to calculate from the sampled leads the instantaneous spatial velocity at each point in time. This transforms the three leads into a single signal, which accen-

tuates the distinguishing feature of the electrocardiogram, that is, the presence of electrical activity during the generation of a complex. The algorithm then uses absolute or relative velocity characteristics of the signal to detect the onset and the end of the various wave forms.

Statistical correlation techniques for fiducial point system: A second method of fiducial point location, which on many occasions is used as a refinement after location by spatial velocity, is the use of statistical correlation techniques. In using correlation, a standard template is somehow defined by the program developer. The template is then correlated against the signal being processed to determine the point of highest correlation. Given the point of highest correlation with the template, the program locates the fiducial point of interest. Even though these techniques are the most prevalent for location of fiducial points, other empirical search algorithms have been defined by various program developers.

Techniques to optimize accuracy of measurements: All of the programs attempt to make use of the redundancy of complexes available in the sampled electrocardiogram to optimize the accuracy of measurements extracted from the tracing. Three techniques are currently in use. The first locates the "best complex" for analysis. To find the "best complex," all of the complexes of a given lead set are located. The program then chooses one of them for analysis. One criterion for the complex selection is generally a function of noise measured on the complex. The second technique locates all of the complexes within the lead set and averages them. This procedure reduces the random noise on the signal. The measurements are then extracted from that average complex. The third technique extracts measurements from every complex located on the lead set and subsequently averages the measurements. It should be noted that in these last two averaging techniques, morphologically different complexes are used neither in averaging nor in measuring. Only those complexes having similarity are used in either averaging the measurements or computing a final "averaged complex."

Because many of the errors attributed to electrocardiographic programs result from measurement errors, evaluation of this function is crucial in determining overall program performance. One difficulty in constructing a measurement program has been the need to define quantitatively qualitative parameters (e.g., S-T shape).

Interpretation

Criteria classification: Classification strategies used by program developers are divided into two major techniques. The first and most widely used is a deterministic approach, that is, the use of Boolean logic statements combined with a decision tree. In this approach, the program follows a logical decision path to ultimately arrive at a set of nonconflicting statements about the electrocardiogram. The second strategy uses maximal likelihood statistics to calculate probability of a particular classification. This technique uses general statistical properties of the measurements with underlying statistical models to develop a better technique for classification of the electrocardiogram. Even in this method, decision trees and some Boolean logic are also invoked before final application of the Bayesian statistics.

Criteria versus measurements errors: The programs using only decision trees and Boolean logic differ from one another primarily in methodology of implementation; that is, it is theoretically feasible to take the logic from any one of these programs and implement it in another program by changing the methodology of implementation to correspond to the second program. Therefore, in evaluating the deterministic programs, it is much easier to differentiate errors in criteria from errors in measurement.

Rhythm Analysis

Rhythm strip analysis: Different rhythm analysis programs are most distinguishable by the amount of data and continuity of those data used by the program. The amount of data analyzed by the programs ranges from 8 second to 60 second strips. In some programs, the rhythm strip is a continuous rhythm strip from a single lead set; in others, the rhythm strip consists of short strips from various lead sets joined together to form a single continuous strip. The latter is used by most of the 12 lead systems; that is, the rhythm strip is constructed from the four lead sets transmitted to the computer, with each lead set being sampled for approximately 5 seconds, giving a total of 20 seconds of rhythm data. With the three lead systems, an 8 to 30 second continuous lead strip is analyzed. Programs using a switched lead rhythm strip have had to devise an algorithm that is independent of the data recorded during the switching intervals. If the data recorded during the switching intervals are not constructed, the difficulty in developing an adequate rhythm analysis program increases as the time of each lead set decreases. A lower limit of 5 seconds per lead set is recommended for such programs. The basic wave form location techniques in the rhythm module are similar to those that are used in the measurement module, with new variables being added to aid in rhythm determination.

Three questions to be resolved by any rhythm analysis program designer are:

1. What is the definition of R-to-R irregularity?
2. How is it possible to search for P waves and over what area?
3. What criteria are available for detection of premature ventricular complexes?

Whereas measurement and classification sections of computer programs have many similarities, with rhythm analysis there is a much greater degree of individuality in the programs. The methods used to answer the preceding questions vary widely among the programs. For example, regularity might represent percentage deviation from the mean R-R interval in one program and be defined as the width of a histogram of R-R intervals in another. Even greater differences characterize the P wave searches devised by the program developers. The differences in approach result primarily from the qualitative nature of the definition of the concepts. Each program must therefore be evaluated separately respecting the effectiveness of its techniques for rhythm determination.

Serial Comparison

Comparative programs: Development of programs for comparative analysis of serial electrocardiograms is still new. The majority of programs available do not yet have a comparative analysis module. The principal difficulty to be resolved by comparative programs is the inconsistencies resulting from measurement changes and statement variations between the two electrocardiograms being analyzed. In deterministic programs it is quite possible to see rather significant differences in the statements reported on serial electrocardiograms, whereas in fact the measurements determined by the program in each of the electrocardiograms do not differ significantly because of the thresholding nature of the decision strategy. As measurements fluctuate about the threshold, statements change. Thus, the program developer is faced with a dilemma of how best to report this information to the user. Each of the programs available with comparative

modules has attempted to handle this problem, with the developers basing their criteria for significant changes in measured variables on their experience and data available to them. These programs are in their infancy, and important changes can be expected during the next few years.

Other General Considerations

Several program characteristics that differentiate electrocardiographic programs do not conveniently fit into one of the preceding modules. These include the amount of analog or digital filtering (or both), sampling rate and precision of digital values. Each of these factors affects the performance of a program and its ability to measure various components of the electrocardiogram. Another consideration is the performance of the program in the presence of noise in the electrocardiogram. The noise rejection criteria of these programs differ significantly and will affect the overall performance of such programs.

A final difference is the use and effect of other clinical data on the outcome of the program. The amount and use of clinical data vary with the clinical status. It is expected that future program development will place increased reliance on clinical data.

APPENDIX II

SYSTEMS AND HARDWARE CONSIDERATIONS

The hardware and software components and the several functions involved in computer analysis of electrocardiograms are illustrated in Figure 1. The reader is referred to the A. D. Little report[2] for a general description of these functions. The following discussion will concentrate on a "typical" system, recognizing that numerous options are available at every electrocardiographic processing step. Deviations from the "typical" system will be pointed out and desirable enhancements to present systems indicated.

Record Identification

Usually, identification information is transmitted over telephone lines from the remote location to the central computer. Two exceptions should be noted: (1) off-line acquisition, where the identification and the electrocardiographic signals are recorded on magnetic tapes or cassettes built into the cart, and later batch-processed by computer; and (2) processing of identification and electrocardiographic signals in a computer and generation of a report on a printer, both of which are built into the cart. The second, a radically different approach, lacks some of the editing, reviewing, storage, retrieval, billing and other desirable features discussed later. But the sharp decrease in the cost of micropressors and other electronic components may make this approach economically attractive in the future.

Identification data to be transmitted: The telephone connection may be achieved through manual dialing or automatic dialing performed by the cart; once established, the identification information is transmitted digitally to the computer. This information may have been present in the cart prior to the telephone call and then transmitted automatically or it may be entered during transmission. It is usually required that a patient identification number be provided as well as a hospital (or department) identification number so that the computer will know where to send the report. It is very useful to include a cart identification number and a technician identification number to aid in isolating problems. Some of

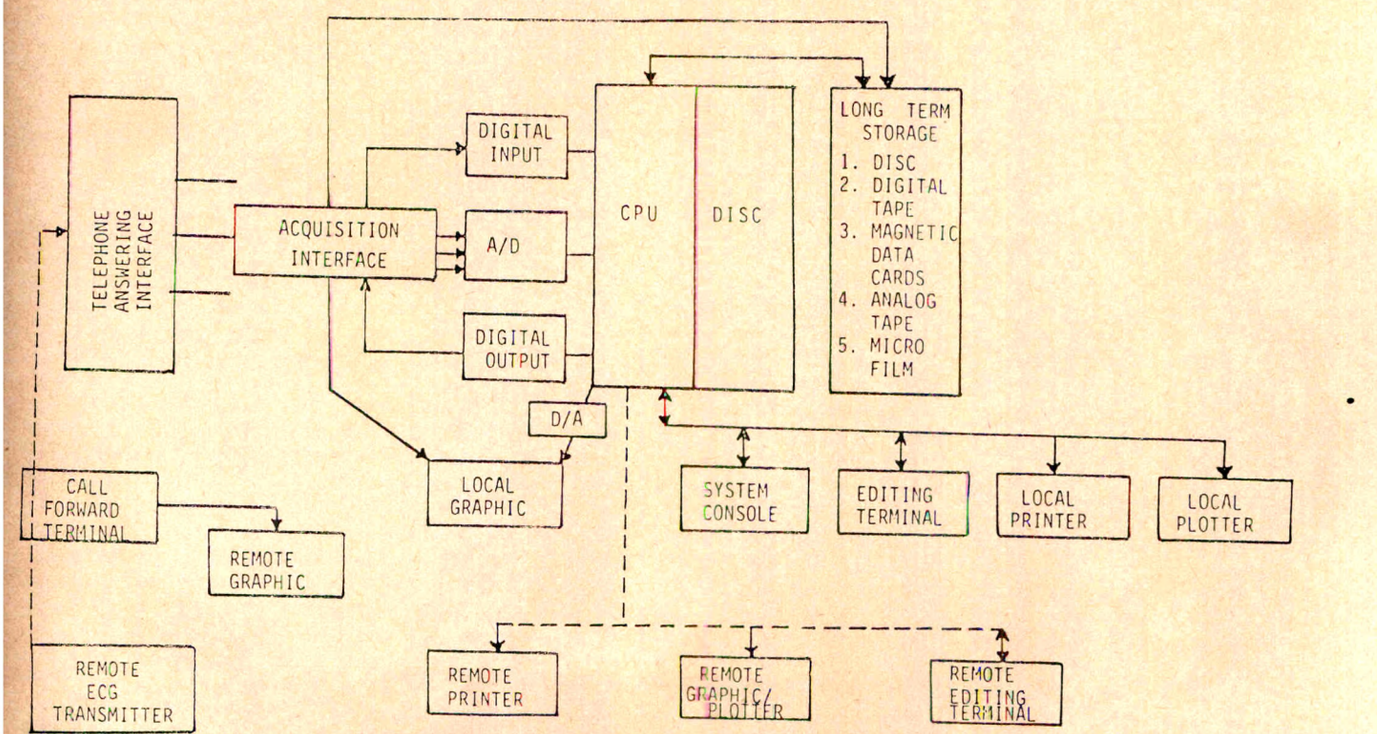

FIGURE 1. Schematic diagram of computerized electrocardiographic analysis system. A = analog; CPU = computation unit; D = digital; ECG = electrocardiographic.

these numbers may be built into the cart so that they don't have to be reset from patient to patient.

There is no consensus on the additional data that should be transmitted as part of the identification sequence. Some of the most popular entries are age, coded medication and diagnosis, height and weight or coded body build, and blood pressure. In off-line systems, the time and date of the electrocardiogram are also very desirable, whereas in on-line systems they are supplied automatically by the computer. If the system has the capability of transmitting letters as well as numbers, the name of the patient, a desirable component of the final report, can be transmitted as well. Because of the lack of consensus the system should be flexible.

Error checking and correction: Because storage and retrieval systems are very dependent on the accuracy of the identification information for ensuring that a series of electrocardiograms belong to the same patient, error checking, and to some extent error correction algorithms, are very desirable. Some examples would be (1) limit checking on variables such as sex, age, blood pressure; (2) the transmission of a check digit at the end of the digit string to serve a function analogous to the parity check bit; and (3) the checking of the patient's age and sex or possible name if there is a minor difference in the identification number relative to a previously stored electrocardiogram.

As errors are detected, the technician should be informed by a signal to the cart and a correction requested. The systems that attempt to improve the quality of the identification information and reduce the price of the transmitter cart by providing voice communication between the electrocardiographic technician and an operator at the computer site will increase the labor and telecommunication costs. Provision should also be made for error detection when the system is in "back-up" mode.

Acquisition and Transmission of Electrocardiograms

In almost all systems, the transmission of the electrocardiographic signals follows after the identification information phase. The signals from the electrodes that had previously been attached to the patient are amplified and combined in the cart to generate scalar leads, and are transmitted automatically, three simultaneous leads at a time, although some systems transmit one lead at a time. These analog signals are modulated for transmission over the telephone lines. (Detailed transmission characteristics, frequency response, and other data are discussed in the report by Task Force II on Quality of Electrocardiographic Records.)

Transmission systems: Some manufacturers convert the signals from analog to digital in the cart before digital transmission, thus eliminating modulation, demodulation and transmission distortions but requiring a buffer in the cart or special telephone lines and modems or data compression schemes. The transmission method affects the flexibility, availability, and cost of access to the central system, and voice grade telephone lines will, in many cases, be most desirable. Analog vs. digital (and, by implication three channel versus single channel) transmission should be analyzed in this context.

The computer receives the analog signals through an interface system, which demodulates and digitizes them (usually at a sampling rate of 250 to 500 samples per channel per second with an 8 to 12 bit resolution). A calibration signal transmitted prior to or after the electrocardiographic signals is used to calibrate the signals and to examine their overall quality. Different systems provide other checks on the signals, such as the length of time each lead set is transmitted; these checks should be easily changed because of the differing requirements of analysis programs.

Signal preprocessing and manipulations: Identification and possible improvement or correction of electrocardiographic signal quality in terms of noise, flat leads, baseline wandering and other artifacts have a major impact on the diagnostic accuracy of analysis programs. The boundary between these signal preprocessing functions and signal manipulation within the analysis program itself is not clear in present programs; however, this is crucial, because the system should decide before disconnecting the telephone whether the electrocardiogram should be accepted. In systems with report printers in the electrocardiographic cart, the cart may remain connected by telephone until an analysis is transmitted back and the technician can then decide whether to retransmit, but in systems where communication is terminated at the end of the transmission, an on-line quality control program should inform the technician through a visual or audible signal that the electrocardiogram was acceptable so that the patient may be disconnected with the assurance that an analysis will be generated.

Report

The electrocardiographic interpretation provided by the computer in the form of a report is usually transmitted by telephone to a remote printer or printed at the computer or review site. In some cases, the report is hand-carried or mailed to the remote site. The report contains the patient number and other identification information from the cart as well as a diagnostic interpretation and selected electrocardiographic measurements. It may also contain a graphic presentation of the complete electrocardiogram or selected portions of it or vector loops.

The report may be generated at the remote site very shortly after transmission or after it has been reviewed by a physician (this activity will be discussed in the next section). Although usually a hard copy report is needed for inclusion on the patient's medical record, under some circumstances, particularly in hospitals having their own computer systems, it may be advantageous for a defined group of users to have access to reports through video terminals.

Unit record: It would be very desirable to have a "unit record," that is, a piece of paper containing all information relevant to the electrocardiogram, rather than the inconvenient package produced by the present systems and caused by the manual matching of the tracing to the interpretation report. If the name of the patient also needs to be typed on the report, additional clerical procedures and delays are created. The machine in which this unit record is generated needs to be able to type and plot with acceptable accuracy and speed while receiving its information from the computer over telephone lines. However, the main difficulty in the compression of information is the length of paper generated by programs, some of which require 30 seconds of electrocardiographic data. The solution is to (1) present it in more than one sheet or in one larger sheet, (2) reduce the scale of the tracing, or (3) present less than the complete tracing by selecting one complex from each lead, or half of each lead. In this case, a continuous strip would need to be presented to illustrate arrhythmias.

Data Management

To facilitate the peripheral activities related to electrocardiographic interpretation, a central computer system should generate a number of reports in addition to the expected interpretation report.

Report on status of different computer tasks: The first of these should be a report that can provide for the central facility, for each remote user of the central system, for each department in a large hospital, for a particular patient or specific electrocardiogram, the status of the different tasks that have been completed for each electrocardiogram, the time at which they were completed and the ones remaining to be completed. Some important questions would be the time the electrocardiogram was received, the time it was analyzed, whether an unconfirmed report was transmitted, whether it was reviewed, whether an edited report was transmitted, and so forth. A natural consequence of this capability is to produce a count for each user of the services performed in a given period of time to serve the billing function. This program can also produce utilization reports of the central facility and provide peak load indications (in time of the day or specific days) when the frequency of electrocardiograms transmitted increases beyond acceptable limits and causes conflicts or an increase in turn-around time.

Report on number of rejected electrocardiograms and corrected interpretations: Another type of report should analyze the number of electrocardiograms rejected from each location and the cause of rejection. If individual carts and technicians are identified in each transmission, specific problem areas can be pinpointed and resolved by correcting telephone line problems, repairing faulty equipment or retraining personnel. A quantitative estimate of the program/physician agreement could be obtained by recording the number of electrocardiograms in which diagnostic statements or measurements are corrected by the reviewing physicians. Information on the type of diagnostic abnormality, the specific measurement and the physician making the correction can be accumulated to point out areas of weakness in the program or possibly differences in clinical criteria between the program developers and the clinical users.

Storage and Retrieval

The storage and retrieval systems provide an extremely valuable resource for research in electrocardiography. A search program should be capable of selecting from the files interpretation reports, tracings or wave forms of electrocardiograms having a particular diagnostic abnormality, belonging to patients using a specific drug or in a given group, and so forth.

Storage techniques: Various storage techniques have been available for some time, such as microfilming of tracings and reports, storage of tracings on analog or digital tape and of reports on digital tape, and the storage of electrocardiographic signals on cards that contain a strip of analog tape. Most of these techniques are limited, either because the stored record is not readable by the computer or because there is significant difficulty in retrieving a desired record. Although they have many advantages, particularly space reduction, over paper systems, they have not been adequate as a basis for automated storage and retrieval systems.

Serial analysis programs: Recent developments in disc storage technology and the availability of computer programs to perform the serial comparison of electrocardiograms promise to provide a new dimension in computerized electrocardiography as well as cost reduction. Very little experience has been gained yet on the utilization and effectiveness of on-line computerized storage and retrieval systems with or without serial analysis programs to formulate a judgment, but many users agree that it has great potential.

The storage needs for human performance of serial analysis are probably different from those of computer programs. Human readers probably require previous computer tracings or at least a single complex per lead plus a rhythm strip, whereas the computer program may require only a "measurement matrix" plus a list of the "diagnostic statements."

Considerations of how much data to store per electrocardiogram are still relevant, and data compression techniques are discussed as ways of optimizing on-line access to a reasonable number of records. The rapidly changing technology may obviate these considerations by providing bigger, faster and cheaper mass storage units in the future.

Physician Review

The computer-generated report can be annotated and edited with the assistance of the computer to improve the final report. This improvement might consist of the inclusion of the patient's name or a verification of the patient's sex, age, medication, or other data. But the most important editing function is that of reviewing, which consists of correction by an electrocardiographer of errors in the computer interpretation of the electrocardiogram.

Reviewer editing of tracing and interpretation: To perform this function, the reviewer needs a complete or a partial tracing, the computer interpretation and possibly other clinical information. If the reviewer is located at the computer site, these are easy to obtain, although in many systems tracings are not routinely generated on all electrocardiograms, so that some action needs to be taken to generate a tracing for editing. If the reviewer is located away from the central computer and away from the transmitting carts, some systems provide a call-forward interface, which receives a call from the transmitting cart and reroutes the call to the central computer, but generates a tracing while the electrocardiogram is transmitted from the remote hospital through it to the central computer. An alternative in this case would be for the remote hospital to transmit the electrocardiogram to the central computer, and for the computer to transmit both a tracing and an interpretation to the remote reviewer. This alternative allows the reviewer to monitor the quality of the signals received by the computer. The reviewer can then compare the tracing to the computer interpretation and (1) enter corrections and additional annotations through a remote editing terminal and request that the edited report be transmitted to the hospital from which the electrocardiogram was transmitted, or (2) call the physician at the transmitting location directly. The task of editing should be made easy, because it requires interaction between the computer and people who do not regularly use computers.

Flexibility and Reliability

Flexibility: Flexibility is needed because no system will satisfy all needs. Some users prefer one analysis program to another; therefore different quantities or types of data may be required, resulting in different transmission requirements (for example, not all transmitting carts are compatible with the same central facilities).

Even within a system that provides a specific analysis program, users have different needs; some users may require editing of all electrocardiograms, but others may require no editing or editing only of electrocardiograms with certain abnormalities. Similarly, some users require additional tracings, vector loops or reports including measurement matrices. Some want individual reports back immediately; others prefer to have them transmitted back as a group. Users also have differing preferences as to the type and amount of data to be kept in a storage and retrieval system for various types of

patients or electrocardiographic abnormalities. A system should satisfy as many of these requirements as possible without having to do major reprogramming of its software.

Reliability: The most important measure of reliability is the percent of time that the central facility is available to the user. This availability requires first, that the central facility be "up," and second, that enough incoming telephone lines be available so that the user can enter the system when necessary. Only the large analysis centers have been able to afford computer redundancy to achieve reliability, but because of cost reductions in computer hardware, a system containing multiple central processing units, discs, acquisition interfaces and other modules may be economically feasible in the future. On the other hand, as more regional centers become operational, it becomes desirable for centers to agree to process electrocardiograms sent from users of another center having hardware problems. Problems would then arise from centers having slightly different versions of the analysis program or from a center not having previous electrocardiograms from the other center to perform serial analysis. Short periods of computer unavailability can be easily resolved by analog recording of the incoming electrocardiograms followed by a batch processing after recovery. There should be a provision to at least acknowledge and record transmitted electrocardiograms in the event of failure of crucial system components.

Power and cart failures: Computer systems should be equipped with automatic hardware and software capability for restarting after power fluctuations or failures, with only the electrocardiogram being received at the time of the failure being lost. The technician sending the electrocardiogram would either be notified that retransmission was necessary or, in the case of total system failure, would be alerted by failure to receive the normal acknowledgement. In addition, the system should be structured so that vital functions can be maintained even when part of the system fails.

Another aspect of system reliability is illustrated by failures of the transmitting cart. In many small hospitals, only one cart is available, and this failure causes total unavailability of the analysis service. Immediate repair or installation of a functioning cart is essential to maintain the confidence of the clinical staff in the computerized system.

APPENDIX III
SYSTEM EVALUATION METHODS

Methodology of Program Evaluation

Evaluation of electrocardiographic programs should be considered in light of the goals of the evaluation. Two primary goals have been identified. The first is measurement of program's diagnostic accuracy (that is, ability to identify properly patient condition). The second goal is to measure the usefulness of the program in a specific environment.

Recently a host of invasive and noninvasive procedures have become available, which allow more extensive documentation and validation of electrocardiographic interpretation than has been possible in the past. As part of this development, there has been a trend in the last 20 years to use the electrocardiogram in more quantitative terms rather than for purely qualitative and descriptive cardiac evaluations. The widespread use of statistical techniques in modern medicine has reinforced this trend toward quantitation, and diagnostic criteria are now being judged by their sensitivity and specificity rather than by strictly empirical subjective clinical experience. This holds true also for the evaluation of interpretation programs.

Methods of Evaluation of Program Accuracy

Three basic methods are here identified for measurement of program accuracy. Method I attempts to determine the sensitivity and specificity of diagnostic classification by a computer using as a standard the electrocardiogram-independent evidence (such as autopsy documentation of left ventricular hypertrophy). This method inherently minimizes observer bias and evaluates the program's true ability to diagnose properly a given set of conditions. *Method II* accepts as a standard a constrained human observer, the constraint being a given set of measurements or criteria agreed upon before the evaluation (for example, conduction defects or arrhythmias).

Method III is similar to Method II, but the constraint is less rigorous. The evaluation in this instance is between the program and the observer, or the majority opinion of a group of observers.

This kind of evaluation should be performed only for descriptive statements, the meaning of which cannot be precisely defined (for example, flat T waves, left ventricular strain). Although it is not possible to use Method I for all measures of program performance, new evaluations should increasingly rely upon it. Similarly, Method II should replace Method III if meaningful comparisons of programs are to be made. It should also be recognized that these same concepts hold true in evaluating physician performance.

Measurement of a computer's electrocardiographic interpretive accuracy in light of these methods results in three types of statements that can be made by human readers or computer programs. The first type (A) comprises statements that refer to the diagnosis of an anatomic lesion or pathophysiologic state and that can be determined from nonelectrocardiographic evidence such as cardiac catheterization studies, serum enzyme levels, ventriculograms, echocardiograms, scintigrams and autopsy findings. The second type (B) covers statements that refer to the diagnosis of an electrophysiologic state and therefore are primarily detected by the electrocardiogram itself. Such diagnoses can at present be confirmed beyond the surface electrocardiographic data only through the use of multiple invasive electrical probes. Statements of Type B, therefore, should lend themselves to evaluation by Method I or II. Statements of Type C are purely descriptive statements of electrocardiographic features, which may or may not be related to anatomic lesions or physiologic disturbances.

Measurements of Accuracy of Type A Statements

Library of cases: To test the sensitivity and specificity of Type A statements, a library of cases must be selected for which the condition has been determined or excluded by nonelectrocardiographic means. Such conditions may be present singly or in combinations. In general, the test library has to have a balanced representation of electrocardiograms from different age groups, races and sexes. Also, the different diseases should be represented in their full spectrum of de-

velopment, starting from the barely identifiable to the extreme cases. All electrocardiograms in the library have to meet minimal quality standards and have to be recorded with equipment meeting minimal technical specifications, for example, those suggested by Wolf et al.[25] Because of their clinical importance, the following diagnostic categories have to be contained in the library: (1) infarction/injury; (2) hypertrophy/enlargement/overload; (3) chronic pulmonary disease; (4) "probably normal," defined as asymptomatic and not positive by nonelectrocardiographic tests for any of the above categories.

Uniformity of criteria and statements: To obtain meaningful results, the testing has to be performed in a multigroup environment. For each of the diagnostic categories the test shall produce results regarding both the sensitivity and the specificity of the criteria. For uniformity, it is recommended that the levels of grading for both the abnormality itself and the electrocardiographic statements be limited to the following terminology (see the report of Task Force I on Terminology and Criteria for definitions):

Normal = definitely, probably

Abnormality = definite, probable, consider

The sensitivity and specificity of each level should be measured in the library.

The robustness of a diagnostic algorithm is measured by (1) its ability to separate a given abnormality from normal, and (2) and its ability to separate a given abnormality from other abnormalities.

It should also be recognized that if a program fails to recognize a documented abnormality, it may be a result of limited information in the electrocardiographic signal itself, not a fault of the program. Further, the signal itself may suggest an abnormality that cannot be documented by nonelectrocardiographic means.

Measurements of Accuracy of Type B Statements

Arrhythmias: *Sufficient numbers of the following rhythm classes should be included:*

1. Sinus rhythm, including tachycardia, bradycardia, and sinus arrhythmia
2. Atrial flutter/fibrillation
3. Premature complexes (atrial or ventricular, single or multiple)
4. Other supraventricular arrhythmias
5. Other ventricular arrhythmias
6. Other less frequent arrhythmias
7. First, second and third degree A-V block

Electrocardiograms for this part of the library should be selected and classified either on the basis of consensus among several electrocardiographers or on the basis of other electrophysiologic studies. In general, performance will be measured by determining the sensitivity and specificity. An exception to this rule is the detection of events that occur rarely because specificity then has only a limited meaning. We suggest an additional measure, the error ratio:

Error ratio = (falsely detected events
+ missed events)/correctly identified events

The output statement "undetermined rhythm" seems to require special treatment. Its frequency of occurrence would be established in each of the preceding rhythm classes, as well as in the total population.

Conduction defects: These are another group of electrophysiologic phenomena for which the surface electrocardiogram is the usual means of diagnosis. In this area, it is sometimes difficult to agree upon predetermined criteria for classification, and further documentation by invasive electrophysiologic studies is rarely available. Sufficient numbers of the following classes of conduction defects should be included in a test library:

1. Bundle branch block (complete, incomplete)
2. Unifascicular and multifascicular blocks
3. Other intraventricular conduction defects
4. Pacemaker rhythm
5. "Normal" as defined in category (vii) for Type A statements by Task Force I on Terminology.

These classifications, even with consensus, may overlap; therefore, it is recommended that testing be limited to measuring the frequency of agreements, partial agreements, disagreements and the frequency of any false calls in the "normal" population.

Measurement of Accuracy of Type C Statements

Type C statements, which describe electrocardiographic features, represent a difficult area for evaluation because they may or may not be related to documentable disease. The differences of opinion may depend largely on local customs and particularly on the place of medical training of the electrocardiographer. When a Type C statement occurs in conjunction with a Type A statement or as a supporting reason for making the Type A statement, it would seem reasonable to regard the Type C statement as part of the Type A statement and not to evaluate that Type C statement separately. However, when an isolated Type C statement occurs, a number of methods for handling it may be considered. Some Type C statements are intended by the program developer to suggest specific diagnostic entities. For example, "increased QRS voltage" may be the developer's way of suggesting hypertrophy. "Left axis deviation from later forces" may be intended to suggest left anterior fascicular block. In such cases, the substitution of a semantic equivalent such as "consider left ventricular hypertrophy" or "consider left anterior fascicular block" should be discussed with the program's developer and treated as Type A and Type B statements. Another approach might be to measure the frequency of the occurrence of such statements in the Type A and Type B libraries, which might suggest where semantic equivalencies might be established.

Test of statements by submission to other electrocardiographers: In the absence of semantic equivalencies or some similar measure of relevence, one could test the acceptability of such statements by submitting a large collection of electrocardiograms, preferably from Type A and Type B libraries, to a large group of electrocardiographers from many different medical centers. Thus one could measure the frequency of occurrence of a given Type C statement (isolated) and the percent of times the expert electrocardiographers agreed with the statement. An isolated Type C statement that had a high frequency but a low percent agreement might adversely affect user acceptance of the program. Similarly, an isolated Type C statement that most electrocardiographers made and for which the program had a low frequency (even though the percent agreement was very high) might also affect user acceptance.

In such a test, it would be useful to supply the human reader with the criteria required by the isolated Type C statement so that he can manually verify from the electrocardiogram that those criteria are, indeed, fulfilled by the tracing. If this manual verification is not feasible or possible, evaluation should consist of enumeration of how many nonverifiable statements the program contains and how often they occur.

It should be acknowledged that such a test is not meaningful when a 3 lead program is compared with statements based on

a 12 lead electrocardiographic program (and vice versa). It is this kind of difficulty that the evaluation methods of Type A and Type B statements are designed to circumvent.

Systems Evaluation

Repeatibility or Reproducibility

Reproducibility and noise factors: Repeatibility or reproducibility of both program measurements and statements is a test of the program's stability in the presence of noise. Commonly encountered types of noise in electrocardiographic records are (1) powerline interference; (2) skeletal muscle noise (electromyogram); (3) baseline wander; (4) telephone transmission noise; (5) digitization noise; (6) other system noise (wow, flutter, amplifier, drift); and (7) patient factors (lead position, for example).

Travis[19] recorded electrocardiograms on magnetic tape and played them back several times. This tests the stability of a program to system noise factors such as wow and flutter. Bailey et al.[20] tested reproducibility by using alternate samples from an electrocardiogram converted from analog to digital representation at a rate twice the nominal rate. A third method, already introduced in 1967[21] and more recently used by Helppi et al.[22] for program testing, superimposes known amounts of random noise on a clean electrocardiogram. This method tests a noise effect somewhat like skeletal muscle noise. A fourth method[23] uses complete repeat recordings from the same patient. This method tests the reproducibility of the program in the presence of all noise factors. The difficulty with this method is that all noise factors, including patient factors, are combined in an uncontrolled way; therefore, one cannot isolate the factor that caused the program to fail.

Some of these difficulties could be avoided if one used very clean electrocardiograms and added controlled amounts of alternating current interference, skeletal muscle noise and baseline wander to the electrocardiographic signal. Since it has been shown by Wolf et al.[24] that different electrocardiographic patterns show different noise sensitivities, the tests described should be performed using noise-free records carefully selected from the different electrocardiographic classifications.

A global figure of merit may be established for comparative purposes for a given clinical environment characterized by the comparative frequency of the different noise types and levels and by the distribution of different electrocardiographic classifications. The program should detect nonelectrocardiographic signal, burst noise, missing leads and inconsistencies in information derived from different lead sets.

Verification of "Translated" Programs

Several electrocardiographic programs have been implemented on computer systems or operating environments that are different from the one for which the program was originally designed. These changes have a distinct possibility of producing program results deviating from the original program developer's intention. Further, systematic differences might even be introduced by different signal preprocessing environments such as signal filtering or characteristics of the analog-digital converters. Users who make such an environmental change should conduct detailed tests to verify the system performance in the altered environment. Documentation of tests and results should be made available.

Evaluation of Other Systems Features

Although the electrocardiographic program determines the clinical utility of a computer interpretation system, other systems features establish the operational utility of the system. Aspects of human engineering will determine the attitude of users toward the new technology. More important still, most of these systems features have a direct bearing on the costs of recording, interpreting and storing of electrocardiograms, and will in a crucial way influence the acceptability of the system.

So far only a few reports are available on the systematic evaluation of total electrocardiographic processing systems,[26] and the methodology for assessing the various features—often of a subjective nature—requires substantial refinement. Methods presented here are therefore of only a preliminary nature.

Operational systems features can be grouped into two categories: (1) Features affecting the convenience of using the system. They are judged by the degree of acceptability by the user. (2) Features influencing the economical aspects of the system. They will be evaluated primarily on the basis of their cost-effectiveness. Items falling under category 1 are acceptance by electrocardiographic technician, acceptance by physician-reviewer, and acceptance by physicians who receive the verified electrocardiographic report.

It is preferable to determine acceptability by all three of these groups after a sufficient period of exposure and familiarization with the system (for example, 2 months). Care has to be taken to not extend the familiarization period too much to prevent possible dissatisfaction from turning into resignation, which might give misleading results.

The evaluation of user acceptance may take two forms, one based on a questionnaire and a second using indirect but measurable quantities. For each of the three groups, the following indirect measures are suggested:

1. **Technician:** The time needed to record an electrocardiogram and perform all the preparatory and clerical functions the system requires is a reasonable measure of the utility of the system. Because this time is also influenced by the degree of the technician's frustration with the system, it provides a measure inversely related to acceptability.

2. **Reviewing physician:** The reviewing physician's role in the system is to edit computer electrocardiographic interpretation so that the result is equivalent to a report he would otherwise produce himself. His system acceptability is influenced by the ease with which he can perform the editing function and by the amount of editing he has to perform. These quantities can be measured in terms of editing time per electrocardiogram and frequency of changes, respectively. The latter quantity should be established separately for the different types and subgroups of statements (such as, Type A, subgroup infarction). It is advisable to perform the acceptance testing separately for individual reviewers, to obtain a measure of variance among the reviewers. No attempts should be made to arbitrate physician reviews to obtain a majority agreement because arbitration will not take place under normal operating conditions. It is emphasized that an acceptance test only evaluates agreement and does not imply accuracy on the part of either the physician or the computer. Even in cases of complete agreement the electrocardiographic interpretation may be incorrect.

3. **Other physicians:** The acceptability of the system by other physicians will be determined primarily by the degree to which the electrocardiographic report facilitates patient management. A second consideration may be the reduction of clerical functions or the addition of special services provided by the system. As an indirect measure of acceptability of the report, one can use the number of consultations with the reviewing physician on patient management. Another, although negative, measure for acceptability is given by the number of inquiries requesting clarification of phrases used in the electrocardiographic report, but this measure can be used only during the very initial phase of the system use.

The evaluation of systems features under category 2 can be performed using standard cost-effectiveness methods. Items in this category include:

1. Elimination of clerical functions
2. Elimination of hard-copy storage
3. Availability of 24 hour service
4. Reduction in paper costs for the several hard copies generally used in interpretation
5. On-line quality control (which reduces number of patient recalls for repeat tracings)
6. Provision of billing services and financial control

A systems evaluation will have to consider all these points and weigh them according to the specific requirements of each installation for a total evaluation of cost-effectiveness.

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Task Force IV: Use of Electrocardiograms in Practice

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Guidelines for Utilization of Electrocardiograms

In addressing the question of utilization of electrocardiograms, continuous ambulatory monitoring and exercise tests, the Task Force considered (1) over- and underutilization, (2) safety, (3) cost, and (4) contribution to diagnosis and patient management. Appropriately supervised, these tests can be performed at an acceptably low risk to the patient. Continuous ambulatory monitoring and exercise testing are expensive, and overutilization may contribute significantly to an excessive economic burden.

A particular concern was that overutilization of these tests may lead to overreaction in the form of unwar-

ranted diagnostic and therapeutic interventions. The Task Force was particularly concerned with inappropriate interpretation of these tests. The tests cannot be interpreted in a vaccuum. They must be correlated with the clinical setting and integrated with the patient's history, physical findings and other laboratory results.

Adult 12 Lead Electrocardiogram: Indications

1. Electrocardiograms are indicated in patients who have clinically suspected heart disease or who are at high risk of having heart disease. Subsequent electrocardiograms may be indicated to evaluate a change in symptoms or clinical status or to evaluate therapy. It is uncertain how often follow-up electrocardiograms are indicated in patients with heart disease whose condition is stable. The Task Force recognized that in some patients periodic electrocardiograms are helpful and that this decision should be left to the judgment of the physician.

2. *Should every adult have a baseline electrocardiogram?* Data are not adequate to establish an age at which electrocardiograms are justified for asymptomatic persons. Cost factors and the problems of unwarranted anxiety produced by misinterpretation must be considered in light of the value of a baseline tracing for comparison with an electrocardiogram taken upon the appearance of symptoms. Nevertheless, the Task Force recommended that a baseline electrocardiogram be obtained in all adults.

3. *Routine annual electrocardiograms*[1] *after a baseline tracing* has been obtained are not indicated unless clinical changes suggest heart disease or the patient is in a high risk group. Routine annual electrocardiograms may be indicated in patients at high risk of having heart disease. In others, periodic electrocardiograms every 5 years may be desirable although there are no hard data to support this recommendation.

4. *In preoperative patients* the Task Force recommended that routine electrocardiograms be obtained in all adults to provide a recent baseline record to help manage surgical complications (for example, cardiac or pulmonary complications, electrolyte imbalance).

5. *In patients with acute myocardial infarction,* daily or several daily 12 lead electrocardiograms are recommended until the condition is stable. In patients with uncomplicated acute myocardial infarction, it is not necessary to obtain daily electrocardiograms after stabilization. It was recommended that an electrocardiogram be obtained shortly before the patient's discharge from the hospital, at his first follow-up visit and before he returns to work or to his previous level of activity.

6. *For patients after cardiac surgery,* guidelines similar to those outlined in the preceding paragraph should apply.

7. *With respect to electrocardiograms in the emergency room,* the Task Force was concerned about overutilization. It was emphasized that electrocardiograms in the emergency room should be indicated medically and should be obtained in conjunction with a careful clinical evaluation that suggests heart disease. When electrocardiograms are performed in the emergency room, a competent electrocardiographer should be quickly available. Comparison with previous electrocardiograms should be encouraged. A tracing taken in the emergency room should be processed and interpreted in the same way as other electrocardiograms taken in the hospital. It should be emphasized that a normal electrocardiogram does not exclude an acute myocardial infarction or any other acute cardiovascular catastrophe.

Electrocardiograms should be obtained in all patients with either penetrating or nonpenetrating chest trauma.

Continuous Ambulatory Monitoring in Adults[2,3]

The clinical significance of much of the data derived from continuous ambulatory monitoring is still unclear and should be considered a focus for additional research. Such recordings are subject to a host of artifacts, many of which may simulate cardiac arrhythmias and ischemia.[4] There is a significant risk of overutilization of such data in the clinical management of patients. Continuous ambulatory monitoring should not be performed without obtaining a 12 lead electrocardiogram.

Indications: Continuous ambulatory monitoring is important in assessing the efficacy of treatment in selected patients with symptomatic arrhythmias or conduction disturbances. The method is also useful to evaluate patients with daily or frequent, rather than occasional, symptoms and to identify possible occult arrhythmias or conduction defects. This should be done in association with a careful clinical evaluation for noncardiac causes of these symptoms. Continuous ambulatory monitoring information should be correlated whenever possible with a diary of the patient's symptoms.

2. Continuous ambulatory monitoring may be useful to evaluate patients who have premature ventricular complexes or ventricular tachyarrhythmias, or both, after a myocardial infarction. The procedure may identify patients with increased risk, but it is not known whether therapy will alter the prognosis of these patients.[5]

3. *The role of continuous ambulatory monitoring to evaluate asymptomatic patients for conduction defects* (for example, atrioventricular or bifascicular block and other intraventricular conduction disturbances, and in follow-up of patients being maintained with pacemakers) is unclear because the value of therapeutic intervention in such patients remains uncertain. This role of continuous ambulatory monitoring needs further research.

4. *Continuous ambulatory monitoring should not be used for routine evaluation of patients with chest pain or discomfort* because ST-T changes observed during continuous ambulatory monitoring are unreliable indicators of myocardial ischemia. Such changes may be observed in many subjects who do not have heart disease.[4,6–11] Continuous ambulatory monitoring is not a substitute for exercise testing.[6–11]

5. *The optimal lead placement* for continuous ambulatory monitoring and the justification for multiple channel continuous ambulatory monitoring require further study.

Exercise Testing in the Adult

The Task Force believed that results of exercise testing may be overinterpreted, leading to unwarranted invasive and therapeutic interventions. An abnormal exercise response alone, without other clinical indications should not be considered a circumstance requiring selective coronary arteriography. Similarly, other costly or formidable procedures should not be considered automatically indicated in asymptomatic subjects

Indications: 1. *In asymptomatic patients,* exercise tests usually do not need to be performed or repeated if there are no clinical indications for the tests including the development of circumstances implying increased risk of significant disease. The Task Force emphasized the difference between exercise electrocardiography and exercise function or tolerance testing. Much information is obtained by the latter, which includes not only the exercise electrocardiogram but also the comprehensive monitoring of symptoms, signs and circulatory responses.[12,13]

2. *To clarify a diagnosis of coronary heart disease,* the patient's clinical status should be carefully assessed before he is subjected to exercise testing. The test may be contraindicated in some patients, such as those with unstable angina; it is also contraindicated within 10 days of acute myocardial infarction.[12,14] Low level exercise tolerance evaluation may help to define exertional constraints for the patient upon discharge from the hospital.

3. *In patients with an abnormal baseline electrocardiogram,* the exercise electrocardiogram has a decreased reliability.[12,14] This applies to patients with ST-T changes on standing, patients with hyperventilation and patients taking drugs (such as digitalis preparations) that may modify the ST-T response to exercise. Patients with electrolyte or metabolic abnormalities may also have ST-T changes during exercise that are difficult to interpret.

4. *After cardiac surgery,* exercise testing is useful to measure the patient's effort tolerance and to evaluate his or her cardiac function. In such postoperative patients, the ST-T changes during exercise testing are less reliable than the assessment of functional and circulatory responses.

5. *Exercise testing may also be useful in following up the status of patients with documented heart disease of many types,* especially after recovery from myocardial infarction. Exercise testing is useful to evaluate the efficacy of treatment in selected patients with cardiac arrhythmias and may complement continuous ambulatory monitoring.[6–11]

6. *Exercise testing is useful to identify some patients with coronary heart disease who are at unusually high risk of having an acute event.*[15] During low levels of exercise, such patients may show marked and early onset S-T segment depression, a decrease in blood pressure, serious ventricular arrhythmias or prolonged postexercise S-T segment depression.

7. *The value of exercise testing in asymptomatic subjects* requires further study. Such testing may be indicated to evaluate subjects (airline pilots, for example) who present an increased community or occupational hazard.[16] Exercise testing is also useful in middle-aged persons before they undertake high level exercise training programs.[17,18]

The Task Force emphasized that exercise tests should be conducted in accordance with safety standards as recommended by the American Heart Association Committee on Exercise. The Task Force recommended progressive multistage exercise testing and recognized the need for further studies concerning optimal lead systems, protocols and computer assistance in interpretation of data.

Pediatric Electrocardiography

Leads: In addition to the usual 12 leads, lead V_4R or V_3R should be recorded routinely. When dextrocardia (cardiac malposition) is present, equivalent right chest leads should be taken. Multiple chest leads (V_4R or V_3R, V_1 to V_6) may not be practical in small babies because of the size of the chest. In these instances, at least the following leads should be obtained: I, II, III, aVR, aVL, aVF and V_4R or V_3R, V_1, V_3 and V_6.

Although much information is available concerning the normal limits of the infant's and child's electrocardiogram in relation to age, sex and race, this is an area for further study.[19,20] A baseline electrocardiogram is not considered necessary in normal children. Routine preoperative electrocardiograms are not indicated.

Indications for electrocardiography in children: These include clinical suspicion of heart disease, chronic anemia, neuromuscular disorders, metabolic disorders, chronic pulmonary diseases and electrolyte imbalance.

The electrocardiogram is also used to monitor possible cardiotoxic effects of antineoplastic drugs and to assess siblings of patients with idiopathic hypertrophic subaortic stenosis (hypertrophic obstructive cardiomyopathy) and other familial heart diseases as well as siblings of patients with a prolonged Q-T interval of unknown cause and children with congenital deafness.

Interpretation: The electrocardiogram in teenagers must be interpreted with caution[21] because even in the absence of recognized heart disease the records frequently show (1) large QRS voltages that can be misinterpreted as evidence for left ventricular hypertrophy, (2) early repolarization with S-T segment elevation that could be misinterpreted as pericarditis or myocardial ischemia, or (3) T wave inversion in leads V_1 to V_3. Accordingly, electrocardiograms in otherwise healthy teenagers with atypical chest pain may be of limited value.

Continuous Ambulatory Monitoring in Children and Adolescents

These tests may be used to unmask conduction defects and ventricular tachyarrhythmias in patients with

cardiac symptoms including syncope and to evaluate atrial or ventricular tachyarrhythmias during physical activity, supraventricular arrhythmias in children who have had extensive intraatrial surgery, sinus bradycardia in the symptomatic child, the therapy of arrhythmias, and children with heart block or with pacemakers. Further study of the value of continuous ambulatory monitoring in children is needed.

Exercise Testing in Children and Adolescents

The same precautions, indications and contraindications should be used as in exercise testing in adults.

Indications: Exercise testing may be used to assess the progression of severity of left ventricular outflow obstruction,[22] including subvalvular, valvular and supravalvular aortic stenosis, coarctation of the aorta and idiopathic hypertrophic subaortic stenosis; to unmask arrhythmias or conduction defects in specific high risk symptomatic patients[23] after ventriculotomy; to detect persistent arrhythmias after extensive intraatrial surgery and to unmask arrhythmias in symptomatic patients.

Comments: It is probable that exercise testing is underutilized in children and adolescents. There is great need for further study to establish indications and normal limits.

The value of the test should be established in children and adolescents with (1) a strong family history of early death from coronary heart disease, (2) hyperlipoproteinemia, (3) hypertension, (4) syncope or near syncope, (5) chest discomfort or pain, (6) asymptomatic arrhythmias, (7) chronic anemia, or (8) mitral valve prolapse.

The value of exercise testing before participation in competitive sports is unknown.

Assessing Competence and Education in Electrocardiography

Electrocardiographer's Competence

The definitive interpretation of the electrocardiogram should be made by a physician (MD or DO).

Electrocardiographers' activities involve three levels: physicians recording and interpreting tracings of their own patients; physicians "reading" electrocardiograms for hospitals, clinics or other physicians, thus acting as consultants, and physicians whose chief interest is in electrocardiography and who act as teachers, investigators and experts in electrocardiography. The great majority of electrocardiograms are being interpreted by the "electrocardiographic reader" working under a contract or agreement with a hospital or clinic. The reader's other role is analogous to that of the hospital pathologist or radiologist for whom there are well defined qualifications (certification by respective specialty boards) necessary for the contractual agreement between the hospital and the radiologist or pathologist. Qualifications for electrocardiographers have never been defined. Thus it is imperative that quality control is maintained by requiring evidence of the electrocardiographer's competence. The Task Force recognized the impact of the change in standards for competence in electrocardiographic interpretation and recommended that this change take place expeditiously for 3 to 5 years and without interrupting services that are currently available.

Electrocardiographer's Qualifications

Certification by the Subspecialty Board in Cardiovascular Diseases of the American Board of Internal Medicine (or American Board of Pediatrics for the childhood population) cannot be required for all electrocardiographers. It is important, however, that those who do not have such certification show evidence of competence in the interpretation of electrocardiograms. This evidence requires documentation of formal training (such as rotation through a cardiology service during residency with adequate training in electrocardiography) and continuing experience and learning in this field. Physicians now engaged in electrocardiographic reading may demonstrate the equivalent of formal training by long experience in the interpretation of electrocardiograms or adequate postgraduate education. It is expected, however, that within 5 years all readers will have demonstrated their competence by passing a qualifying examination (to include pediatric cardiology) in electrocardiography. Inasmuch as the subspecialty boards currently do not provide testing and certification in a limited area of their subspecialty, the qualifying test in electrocardiography should be organized by cardiologic educational organizations, such as the American College of Cardiology and the Council for Clinical Cardiology of the American Heart Association. The test should emphasize the interpretation of electrocardiograms together with basic theoretical knowledge.

Because of rapid changes in the field of electrocardiography, the knowledge and competence of all electrocardiographers should also be updated every 5 years after completion of formal residency training. Physicians who complete their residency training and who have adequate training in electrocardiography will be expected to pass the qualifying examination in electrocardiography (or the examination of the subspecialty board in cardiovascular diseases) within 2 years after completion of their formal training.

Criteria for competence of electrocardiographers can best be defined by delineating the essential recommended knowledge and skills. Such an enumeration, undertaken by an ad hoc committee of the American College of Cardiology with input from 20 well known electrocardiographic authorities, was prepared for the Electrocardiography Core Curriculum and Self-Assessment Program of the College.[24] The list of recommended skills and knowledge is divided into two categories: (1) those for electrocardiographic readers (147 items), and (2) those for the advanced electrocardiographer and teacher (174 additional items).

Electrocardiographic Interpretation in Acute Care Hospitals

Electrocardiography is a laboratory procedure that must be applied and interpreted in the context of the clinical problem. In this respect, it is akin to radiology,

in which the reader acts as a consultant who may interpret the same change differently according to the available clinical information. Electrocardiographic interpretation provided with the knowledge of the clinical problem is superior to and more likely to be correct than that provided on the basis of the tracing alone. Thus, in an acute care hospital it is highly desirable to have available fully trained electrocardiographic readers. However, if electrocardiographers of demonstrated competence are not available, present technology permits telephone transmission of electrocardiograms for interpretation in a distant organized electrocardiographic facility. This system is preferable to having electrocardiograms interpreted by readers who cannot meet standards of competence. Some of these electrocardiographic referral centers or systems are equipped to provide immediate reader interpretation or computer interpretation with overreading.

The Task Force recognizes the considerable potential error in computer interpretation of electrocardiograms and recommends that all computer interpretations, including those read as normal, be verified by a qualified reader. Furthermore, capabilities for comparison of tracings must be available.

Training in Electrocardiography

Training in electrocardiography should include in-depth experience with a wide variety of records and should be based on material from acute care hospitals, in which there is an ample variety of tracings from acute cardiac disorders (myocardial infarction, arrhythmias). It is recommended that all training programs for all physicians performing primary care (in fields such as internal medicine, pediatrics, emergency medicine and family practice) include a formal rotation through electrocardiographic units that provide trainees the learning experience of supervised interpretation of at least 2,000 tracings. Such training, followed by continuing exposure to postgraduate courses and practical experience in electrocardiography, could afford those with outstanding interest in this diagnostic procedure sufficient competence to pass the proposed test.

Periodic continuing education courses should be made available to electrocardiographic readers. The purpose of such courses would be to update electrocardiographic knowledge and review previous knowledge. The postgraduate course or workshop should have specific objectives and a well defined curriculum encompassing the essential knowledge and skills required by the electrocardiographer. The format of continuing education instruction should vary: The programs might be organized, for example, as a concentrated 3 to 5 day course or as a series of sessions held once a week.

Conclusions

Guidelines for the utilization of electrocardiograms in the pediatric and adult age groups interpreted by physicians or by computer programs were defined. Similar guidelines were defined for the use and interpretation of continuous ambulatory monitoring of the electrocardiogram and of exercise testing.

Recommendations were made for a core curriculum in electrocardiography, certification of competence in the interpretation of adult and pediatric electrocardiograms and reassessment of competence at appropriate intervals.

In certain areas it was recognized that no definite recommendations could be made at this time and that additional study was needed.

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Task Force V: Cost Effectiveness of the Electrocardiogram

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This report was designed to survey the available body of knowledge concerning the cost of electrocardiograms and indicate areas in need of further study. The need to establish a reasonable cost is accentuated by the present climate of concern about the cost of health care on the part of the Congress, the legislatures and the public. National expenditures for health care have tripled since 1965.[1] The availability of hard data will allow judgments of reasonable, justifiable charges by administrators, physicians and consumers.

This type of data will be scrutinized carefully in coming years. The passage of the Health Policy, Planning and Resources Development Act of 1974 (P.L. 93-641) and the subsequent designation of health planning agencies throughout the country are an example of establishing agencies to review new and existing health services, to determine if the cost is reasonable and the services necessary.

The establishment of a standardized cost-accounting method for electrocardiograms and cost-effectiveness determinations for various methods of their acquisition will expedite and simplify the procedures for charge justifications. Further, many employers and health insurers, as well as unions, are questioning the high cost of health insurance and pressuring providers to lower costs or provide alternative service delivery methods.

A search of published data reveals that information concerning the cost of electrocardiography is sparse. Those reports that do exist are fragmented, and the populations studied are small or in unusual circumstances. It is vital that the facts about the expenses involved in electrocardiography be established.

Cost-benefit decisions carry the potential trade-off between lower cost and higher quality. These decisions need physician input if they are going to be reliable, safe for patients and accepted by the medical community.

Definitions of Users

The costs of obtaining and interpreting electrocardiograms are dependent upon several factors—volume, rate of normal and abnormal tracings, hours of service and type of equipment used. Table I summarizes some characteristics of various users that influence the costs of electrocardiograms. Users are categorized into three groups: primary, secondary and tertiary care providers.

Data acquisition and processing methods relate to the type of service required. Although a single practitioner performing an average of eight electrocardiograms a day can work efficiently with a single channel recorder, a 1,000-bed tertiary care facility taking 4,000 records a month might justify a dedicated computerized elec-

TABLE I

User Characteristics—Influence on Electrocardiogram

Facility	Type of Patient	Type of ECG (Pathology)	Results Sensitivity/Specificity	Volume per Year	Equipment
Primary Office (private) Group	Outpatient	High number of normal tracings	High sensitivity	100–1,000/year* 2,000–40,000	1 channel 3 channel
Secondary	Inpatient	Balanced Normal vs. abnormal	High sensitivity High specificity balanced	Low–2 per bed/month† High–4 per bed/month 2,500–15,000	74% 1 channel‡ 19% 3 channel 7% 3 channel automated
Tertiary	Inpatient/ Outpatient referral	Normal < abnormal	High specificity	Low High	

* Source: Telemed Inc.
† A. D. Little report.[3]
‡ For hospitals with fewer than 300 beds.

trocardiographic system on grounds of economic feasibility.

Primary care providers usually see a high number of normal screening electrocardiograms; they are not cardiologists and may have limited access to their services. Screening clinics for industry or government process a high proportion of normal electrocardiograms for employment or other special purposes.

Secondary care facilities treat inpatients, most of whom have relatively uncomplicated medical or surgical problems. The size of these institutions ranges from 30 to 600 beds. Because their population consists of inpatients, the ratio of normal to abnormal electrocardiograms is more balanced.

Tertiary care facilities handle complex cases on a regional basis and frequently perform teaching functions as well. They usually have a staff of cardiologists and a larger number of abnormal electrocardiograms for interpretation.

The distinction between secondary and tertiary care facilities is becoming blurred because of trends toward specialization and the displacement of specialists toward secondary care facilities providing a full range of services.

TABLE II

Cost Elements in Electrocardiography

	Manual	Computer	Computer With Overread
Personnel			
Clerical	+	+	+
Computer operator	−	+	+
Physician	+	−	+
Technician	+	+	+
Supervisory	+	+	+
Programmers	−	+*	+*
Space			
Data preparation	+	+	+
Storage	+	+	+
File room	+	+†	+†
Reading area	+	−	+
Computer area	−	+	−
Report preparation area	|	|	|
Copier area	|	|	|
Billing area	+	+	+
Supplies (consumables)			
Billing forms	+	+	+
Dictation	+	−	−
ECG cable sets	+	+	+
ECG cutting equipment	+/−‡	+/−‡	+/−‡
ECG paper	+	+	+
ECG paste	+	+	+
ECG paste wipes	+	+	+
ECG styli	+	+	+
Magnetic storage media	−	+	+
Other storage media	+	−	−
Computer software	−	+	+
General office supplies	+	+	+
Computer supplies, other	−	+	+
Equipment			
Accounting/billing machine§	+	+	+
Computer hardware	−	+	+
ECG recording equipment	+	+	+
Storage media	+‡	+‡	+‡
Reproduction equipment	+	+	+
Typewriter	+	+	+
Furniture	+	+	+
Telephone	+‡/‖	+‡/‖	+‡/‖
Other	+	+	+
Liability insurance, power, heating, air conditioning, other indirect costs			

* Optional—applicable only when program development and modifications take place.
† Optional—computer hardware may serve as only file area.
‡ Depends on electrocardiographic equipment used.
§ Nonessential item—frequently used.
‖ Depends on type of service.
ECG = electrocardiographic.

Method for Electrocardiographic Recording

Electrocardiographic recorders: The elements influencing the cost of electrocardiographic production and processing are listed in Table II. In the United States electrocardiograms are recorded with single or three channel machines. Although six channel recorders are available, they are not yet in wide enough use to ascertain true costs.

The operation of single channel recorders is essentially manual. Several manufacturers provide an automatic lead switch for a predetermined recording duration. Although their performance and reliability are accepted and have been proved over the years, these recorders require more technician time to record and process each tracing than do three channel recorders.

Three channel recorders demonstrate useful and increased productivity, although they cost six times as much as single channel carts. The actual recording time does not differ significantly but the three channel electrocardiographic cart has a distinct advantage in productivity per technician. A technician with a single channel recorder can process 360 tracings a month (computer-assisted practice of cardiology report—CAPOC[2]). The same technician can handle 760 elec-

TABLE III

Comparison between Single Channel and Three Channel Recorders*

Volume of ECG (no)	Single Channel		Three Channel	
	Absolute Cost per ECG ($)	No. of Carts Necessary to Handle ECG Volume	Absolute Cost per ECG ($)	No. of Carts Necessary to Handle ECG Volume
1200	6.06	4	4.80	2
1400	6.46	5	5.47	3
1600	5.71	5	4.84	3
1800	6.06	6	4.80	3
2000	6.34	7	5.27	4
2200	5.81	7	4.83	4
2400	5.72	8	4.46	4
2600	5.96	9	4.85	5
2800	5.56	9	4.53	5
3000	5.51	10	4.25	5

* Data obtained from the CAPOC report.[2] Data represent total direct costs for manual processing. Differences in cost are due solely to differences in type of cart used. All other cost factors are held constant for this simulation.
ECG = electrocardiogram.

trocardiograms a month with a three channel recorder. Three channel carts are being increasingly used in institutions that may or may not also use computer processing.

Volume: The impact of this efficiency factor as it relates to electrocardiographic volume is displayed in Table III. Since the various cost elements are comparable and derive from the same source (CAPOC report),[2] it seems clear that three channel recorders are most efficient for large institutions. Table III shows that the cost per electrocardiogram is significantly affected when volume requires purchase of an additional unit. This phenomenon is less noticeable when volume is large. Hard data to support this analysis for smaller volumes are not available to this Task Force. The dollar figures used in the CAPOC report are derived from government sources and thus are not necessarily comparable with private sector costs. They are shown strictly for comparison purposes.

Computer-assisted costs: An additional point for consideration is the cost of transmission of electrocardiograms from recording site to processing site. Several options are now available: (1) generation of hard electrocardiographic copy to be manually transported to the site or mailed in batches; (2) on-line transmission through conventional telephone lines with storage at the processing site on tape for subsequent batch processing either manually or by computer; (c) recording in magnetic output for subsequent batch processing by direct transmission to the processing site; and (d) on-line transmission and computer analysis.

The cost-effectiveness of three channel recorders, combined with on-line transmission through conventional telephone lines and permanent magnetic storage, is shown in Table IV. Such systems shorten clerical time and report generation if a dedicated minicomputer is used to generate the full diagnostic statements. It can be seen that a 4:1 improvement in average handling time is obtained by changing from 3.67 hours/electrocardiogram to 0.97 hours electrocardiogram. However, this improved efficiency does not result immediately in decreased production costs because a minimal number of technician hours are needed to provide an adequate hospital staffing pattern.

Technician costs: With increasing personnel costs in recent years, this difference in costs may be more impressive. Future studies should document when and whether decreased technician time becomes an important cost consideration. Technicians are still needed, but they can also perform other tasks in their newly freed time. The improved efficiency can be translated into expansion of services, such as provision of more hours of coverage per working day. This improvement in the quality of service can be accomplished with no additional costs. Table V illustrates the impact of semiautomation on cost per electrocardiogram for a 450 bed university hospital (1973 dollars).

Cost Breakdowns for Manual Electrocardiographic Operation

This section analyzes what little cost information is available and indicates areas in which information is inadequate. To determine the actual cost per record, more than the obvious cost of carts and electrocardiographic paper must be acquired. Items such as overhead, space and fringe benefits for personnel are also factors to be considered.

A cost analysis of manual electrocardiographic processing appears in Table VI. Total production costs for varying institutional characteristics are compared. This presents difficulties simply because the cost factors could not be standardized. Furthermore, accounting practices vary among institutions, and it is difficult to establish an absolutely comparable breakdown of cost elements. A study in which comparable costs could be identified would be useful. We did not have the resources to undertake such a task.

We defined three basic cost categories: personnel (technical and supervisory, not interpretive fee), direct expenses (suppliers, equipment maintenance and equipment depreciation) and indirect expenses (space rent, plant operation and overhead).

The cost of an electrocardiogram varies because of factors other than the type of chart or number of technicians available. For example, tracings acquired from groups of ambulatory patients reporting to a central location are less expensive than the same number of

TABLE IV

Operational Statistics (1972/1973)

	System	
	Manual	Semiautomatic
1. no. of ECGs processed per day		
Immediately processed	30	42
Delayed until next day	22	12
Total processed	52	54
2. Average Handling Times		
Holding time/delayed ECG (hr)	7.25	4.0
Queuing time/delayed ECG (min)	7.5	0.8
Processing time/ECG (min)	15.0	1.5
Average throughput time/ECG (hr)	3.67	0.91

ECG = electrocardiogram.

TABLE V

Balance Sheet (1972/1973)

	System	
	Manual	Semiautomatic
Debit		
Capital expenditure (amortized over 5 years)	$ 666	$ 16,200
Operating costs (Manpower, space, expendables and maintenance)	$101,277	$ 99,820
Total costs	$101,943	$116,020
Credit		
System availability (%)	30	66
Average handling time/ECG (hr)	3.7	0.9
Average retrieval time/record (min)	8	2

ECG = electrocardiogram.

TABLE VI

Cost Analysis—Manual Electrocardiographic Processing (physician costs excluded)

	Navy Regional Medical Center San Diego¶		450 Bed Eastern University Hospital	400 Bed Eastern Teaching§ Hospital	300 Bed Eastern University Teaching‖ Hospital†	250 Bed Eastern Community Hospital	University Group Practice	Eastern Medical Center Outpatient Department§
	2 Channel	3 Channel						
Personnel	4.94	3.33	4.41‡	2.22*	2.80*	55011*	3.57*	1.20*
Direct expenses (supplies, maintenance, etc.)	0.68	1.01	2.71	8.17	1.05	8485	1.70	8.17
Indirect expenses	—	—	3.27	3.13	1.35	15,776	2.50	2.79
Total cost per ECG	5.62	4.34	10.39	13.52	5.20	8.84	7.77	12.16
ECG volume	45,312		24,000	25,000	17,500	8,988	2,000	2,900

* Includes percent of time and effort of physician director, when applicable.
† 1974 data abstracted from Automated Electrocardiography in the United States.[3]
‡ Provides technician service 24 hours a day, 7 days a week (as of July 1, 1976).
§ As of January 1, 1977.
‖ 1974 data.
¶ Figures derived from the Department of Defense and private communications.
ECG = electrocardiogram.

tracings taken by a technician in individual hospital rooms. When these scattered orders constitute the bulk of the institution's electrocardiographic caseload, the type of cart, the institution's layout and other factors play an increasingly important role in cost determination.

Analysis of Manual Interpretation

Determining the actual cost of electrocardiographic interpretation is difficult because allocation of the cost of the physician's interpretation can be done in several ways. The type of institution, the interpreter's level of skill, the degree of abnormality of the tracings and the nature of the patient population all influence the time necessary to interpret the electrocardiogram. The cost associated with interpretation by an expert electrocardiographer is higher than that associated with interpretation by a generalist. Adjusting for the cost of such expertise in providing interpretation of complex time-consuming electrocardiograms belongs in a more extensive but necessary study.

Physician costs: The best available method is to assess the potential cost of a physician's providing the necessary electrocardiographic analysis. The data presented here are derived from several sources. The report "Automated Electrocardiography in the United States"[3] indicates that the average reading time for a cardiologist is 97 seconds per electrocardiogram and the range is from 60 to 180 seconds.[3] This means that on the average a cardiologist can process between 30 and 40 electrocardiograms an hour.

The value of the physician's time for interpretation of electrocardiograms can be calculated in terms of his total gross annual earnings or in terms of the fee he charges for each interpretation. Because the fee for service compensation systems are more widely used, it is probably more realistic to calculate costs using these figures.

According to a study of electrocardiographic costs by Arthur D. Little, Inc., fee schedules represent the market price for the cardiologist's time and also indicate a value placed on his responsibility for the interpretation. Annual income figures can be used to calculate the value of the time saved by computerizing electrocardiographic interpretation. However, both methods of calculating costs are very imprecise.

Teaching time: One of the numerous elements in evaluating physician cost is the teaching conducted in most tertiary hospitals or institutions affiliated with medical schools where graduate and postgraduate education is conducted. A study conducted in the Electrocardiographic Laboratory at the George Washington University Medical Center in 1974 estimated that during a 3 month observation period, 48 percent of a cardiologist's reading time was spent in teaching. In other words, when electrocardiograms were read in conjunction with trainees and medical students, the efficiency factor of the cardiologist decreased by approximately 50 percent.

TABLE VII

Range of Internists' Fees for Electrocardiogram With Interpretation and Report*

Fee ($)†	% of Internists Charging It
≥25	17
20	35
16–19	11
15	30
11–14	3
≤10	4
Median fee $20	

* The costs covered include not only those of acquiring, mounting and storing the electrocardiogram, but also the physician's fee for interpreting the record and processing his findings (report). The distinction is important because interpretation costs are sometimes shown separately.
† Fees are those most frequently charged by office-based MDs in the spring of 1975. Fees are shown as single figures instead of as ranges where few if any doctors charge amounts in between; in these cases variations have been lumped with the lower figure. From **Owens A:** At last: hard figures on how fast fees have been climbing. Medical Economics, October 13, 1975, p 109.

TABLE VIII

Cost of Implementation of In-House Computer ECG System

	Cost ($)
Computer systems	
Basic system	100,000–140,000
includes all hardware and software for in-house application	
Approximate monthly rental with maintenance	3,000/month
Yearly maintenance	7,000/year
Typical system	120,000–150,000
(includes basic system plus ability to provide service to remote hospitals)	
Approximate monthly rental with maintenance	3,500/month
Yearly maintenance if purchased	8,600/year
Analysis and storage system	200,000–225,000
(includes typical system plus ability to store 150,000–200,000 ECGs)	
Approximate monthly rental with maintenance	6,000/month
Yearly maintenance if purchased	14,000/year
Program rental fee	400–600/month
Computer-compatible ECG carts	
1-channel writer, 3-channel transmission	5,000
Approximate monthly rental with maintenance	145/month
Yearly maintenance if purchased	400/year
3-channel writer, 3-channel transmission	7,400–9,000
Approximate monthly rental with maintenance	225/month
Yearly maintenance if purchased	700/year
Other equipment	
Remote teleprinter	2,500–3,000
Approximate monthly rental with maintenance	80/month
Yearly maintenance if purchased	250/year
First year of maintenance	Usually covered under warranty

Ratio between normal and abnormal records: The volume of the operation and the ratio between normal and abnormal tracings help to define the most effective method for electrocardiographic analysis. Trained technicians can perform routine measurements and preprocess electrocardiograms with a coding system to facilitate physician work and enhance performance. This approach may prove extremely useful for those institutions not large enough to justify a computer system.

Table VII shows the range of internists' fees for interpretation of electrocardiograms. The figures from a study prepared by the Department of Defense evaluating the Naval Regional Medical Center in San Diego indicate that it takes 2 minutes to interpret a normal electrocardiogram and up to 6 minutes to interpret an abnormal one. Assuming 50 percent abnormal tracings, these data indicate that 50 hours of cardiologist reading time are required per 1,000 electrocardiograms.[3]

Computerized Electrocardiography

Computerized In-House Electrocardiographic Systems

Cost analysis of computerized electrocardiographic processing requires separation of acquisition and processing costs. In general, the implementation of computerized interpretation for hospital use is associated with the use of three channel carts. Additional costs are incurred when remote facilities perform analysis of data because the total charges associated with long-distance telephone calls must be incorporated into the total unit cost.

The cost of a computer system (central processing unit) and related peripheral equipment, currently used for electrocardiographic processing is shown in Table VIII. An expense that in-house computer processing would add is installation of telephone jacks at the patient's bedside to permit on-line transmission, a cost that usually is no more than $20 per installation with no monthly additional charge and a dedicated business line. Any study of cost effectiveness of computer processing requires a clear correlation with electrocardiographic volume (Table IX).

Service Bureau Processing

Commercial service bureaus provide computer-assisted electrocardiographic interpretation for customers

TABLE IX

Monthly Cost of Computerization With In-House System*

	Assuming 5-Year Equipment Amortization	Assuming 10-Year Equipment Amortization
Facilities	$ 340	$ 340
Program rental	400	400
Computer cost	2,530	1,560
Maintenance	800	800†
Total	$4,070	$3,100
Difference in cart cost	50/cart	30/cart
Effect of ECG Volume		
1,000/mo		
Approximate costs/ECG	$4.25	$3.20
2000/mo		
Approximate costs/ECG	$2.20	$1.65
3000/mo		
Approximate costs/ECG	$1.50	$1.15

* Assuming 300 electrocardiograms per cart per month.
† Estimate.
Source: Reference 3, p 80.

ranging from physicians in private offices to the staffs of clinics, hospitals and screening centers. We considered three representative service bureaus whose basic service charges are shown in Table X. As indicated, charges are volume-dependent, with defined break points resulting in user discounts for higher volumes.

Basic charges are based upon a graduated monthly electrocardiographic volume, but differences in what is included as part of this charge make absolute comparison difficult. For example, one service bureau includes either a specialized transmitting device or a single channel tracing recorder with transmitting capability at no charge, but it requires a minimal monthly volume (6 and 15 electrocardiograms a month, respectively). Another vendor can provide graduated schedules including either a three channel cart and a teleprinter or one covering only the analysis service.

Several service bureaus include telephone charges for data transmission to their facilities and for return of the analysis reports. Some require an additional $1 per electrocardiogram to telephone results back to the user. (Their basic charge includes mailing the analysis report to the user.)

TABLE X

Representative 1976 Service Bureau Costs

Company	Channels (no.)	Monthly Volume	Cost/ECG ($)	Cumulative Monthly Cost ($)
A*	3	1–200	3.75	750.00
		201–500	3.00	900.00
		501–up	2.25	
B	3	1–100	4.00	400.00
		101–300	3.50	1,100.00
		301–500	3.10	1,720.00
		501–700	2.85	2,290.00
		701–1000	2.60	3,070.00
		1001–up	2.40	
C	1	1–6	6.00	36.00
		7–24	5.50	135.00
		25–49	5.00	260.00
		50–99	4.75	497.50
		100–199	4.50	947.50
		200–299	4.25	1,372.50
		300–499	4.00	2,172.50
		500–up	3.75	

* Includes long-distance telephone service.

Source: Reference 3, p 45.

TABLE XI

Commercial Service Bureau Options and Associated Costs

Company	Option	Cost ($)
A	Review and overreading by a cardiologist	4.50/ECG
	Serial comparison	4.50/ECG
B	Review and overreading by a cardiologist	No charge—all ECGs are overread
C	Review and overreading by a cardiologist	3.50/ECG
	Review and overreading + serial comparison	5.00/ECG
	Mounting of ECG tracing	0.60/ECG
	Report call back	1.00 including telephone cost

ECG = electrocardiogram.

As a minimum, each user requires at least two local business telephone services in addition to the service bureau charges. Telephone costs include a fixed installation charge and monthly local service charges. In addition, the user ordinarily requires a telephone coupler for his electrocardiographic cart and for the teleprinter used to return the analysis report.

In addition to the basic charges, each service bureau also provides various optional services and ancillary electrocardiographic supplies (Table XI). This is in

TABLE XII

Electrocardiogram with Interpretation and Report: Charge per Procedure for 49 States (no data available for Alaska), District of Columbia and Puerto Rico

State	Average Cost per Procedure ($)	Procedures (no.)
Alabama	19.12	41
Arizona	26.41	162
Arkansas	26.04	297
California	26.44	3,585
Colorado	23.81	32
Connecticut	19.77	30
Delaware	19.82	11
District of Columbia*	49.37*	70
Florida	18.47	680
Georgia	22.18	205
Hawaii	19.91	92
Idaho	30.24	38
Illinois	17.75	12
Indiana	25.65	55
Iowa	35.26	39
Kansas	17.91	11
Kentucky	22.10	30
Louisiana	19.11	158
Maine	22.15	39
Maryland	20.24	137
Massachusetts	26.53	307
Michigan	21.59	85
Minnesota	24.36	25
Mississippi	23.09	32
Missouri	28.82	34
Montana	28.09	44
Nebraska	15.08	119
Nevada	33.23	37
New Hampshire	21.81	26
New Jersey	27.42	57
New Mexico	20.45	28
New York	32.80	152
North Carolina	22.33	66
North Dakota	18.33	3
Ohio	18.37	35
Oklahoma	25.74	163
Oregon	22.58	83
Pennsylvania	23.50	195
Puerto Rico	18.33	3
Rhode Island	23.30	10
South Carolina	13.79	19
South Dakota*	41.75	4
Tennessee	56.71	49
Texas	15.10	177
Utah	24.17	24
Vermont	16.38	16
Virginia	20.14	196
Washington	21.35	141
West Virginia	13.59	69
Wisconsin	26.51	37
Wyoming	23.20	10
	Total	7,970

Office of Civilian Health and Medical Program of the Uniformed Services, Department of Defense, Fiscal Year 1976 (O CHAMPUS).
* Questionable.

TABLE XIII

Data Pertaining to Electrocardiograms Performed During Fiscal Year 1976: Office of Civilian Health and Medical Program of the Uniformed Services, Department of Defense*

Procedure	Cost ($)
Electrocardiogram	
With interpretation and report	24.64
Tracing only, without interpretation and report	17.76
Total number of procedures = 7,970	

* On the average, 22.5 percent is paid by the patients, with the remaining 77.5 percent being paid by O CHAMPUS.

TABLE XIV

Medicare Directory of Prevailing Charges for Electrocardiograms (fiscal year 1976)

State	Average for State ($)
Alabama	18.50
Alaska	32.75
Arizona	20.77
Arkansas	16.27
California	22.43
Colorado	17.23
Connecticut	16.71
Delaware	18.00
Washington, D.C.	20.00
Florida	21.22
Georgia	15.92
Hawaii	20.00
Guam	20.50
Idaho	20.37
Illinois	15.94
Indiana	16.03
Iowa	16.68
Kansas	17.60
Kentucky	15.16
Louisiana	16.18
Maine	16.41
Maryland	20.00
Massachusetts	20.00
Michigan	18.10
Minnesota	18.10
Mississippi	16.30
Missouri	15.64
Montana	20.91
Nebraska	16.76
Nevada	25.20
New Hampshire	16.35
New Jersey	21.10
New Mexico	18.77
New York	23.38
North Carolina	15.00
North Dakota	21.00
Ohio	17.63
Oklahoma	16.58
Oregon	18.46
Pennsylvania	21.07
Rhode Island	20.57
South Carolina	15.00
South Dakota	17.50
Tennessee	15.31
Texas	18.04
Utah	17.50
Vermont	20.00
Virginia	15.78
Washington	21.35
West Virginia	17.31
Wisconsin	23.33
Wyoming	17.70

Source: Social Security Administration, Bureau of Health Insurance, Division of Contractor Operations. Carrier Performance Section, Room 2-0-5 East Building, 6401 Security Boulevard, Baltimore, Md. 21235. Personal communication.

addition to the basic monthly service charges. In essence, when a user is considering a contact with a service bureau, it is imperative to define explicitly what type of service is required, what is included in the service bureau's basic charges, what options are required and what it is the user's responsibility to provide.

Electrocardiographic Charges for Manual and Computer-Assisted Electrocardiographic Processing

Precise information on electrocardiographic cost could not be ascertained. Accordingly, an attempt was made to evaluate the question indirectly by examining charges as reported by major insurance carriers for various states.

Tables XII to XV depict the geographic distribution of electrocardiographic charges for two major providers. Variations are readily apparent for various states with no clear relation to regional area. Charges do not seem to differ significantly between manual and computer-assisted electrocardiographic processing (Table XVI). Similarly, the average charges vary only slightly regardless of the medical environment providing the service. Information concerning charges in relation to the expertise of the interpreter cannot be determined, and it appears that a major cost factor is what the local communities consider customary and reasonable for the procedure, as well as the allowable charge by the largest providers.

Facilities

Space and related facilities needed for the adequate function of a heart station are a direct consequence of the characteristics of the institution and the volume of electrocardiograms processed. The electrocardiographic laboratory should be integrated with the other cost centers involved in noninvasive cardiologic diagnostic procedures if they are available.

Space specifically allocated to electrocardiography is determined by the volume of records processed and the type of processing utilized. Minimal requirements include a comfortable well lighted reading room, office space for the laboratory supervisor, ample storage space for the last 5 years of recordings, appropriate space for the preparation of reports and other administrative support functions (such as billing and preparation of insurance forms) and space for specific

TABLE XV

Electrocardiographic Charges per Region ($)

Region	Charges
East	19.51
South	17.09
Central	17.86
West	21.03

TABLE XVI

Hospital Charges for Manual and Computer-Assisted Electrocardiographic Processing*

Charges	Manual	Computer
High	$30.00	$35.00
Low	15.00	12.00
Average	21.40	21.00

* Modified from Ref 3, p C-4.

TABLE XVII

Electrocardiographic Volume Cost Analysis ($)

	1 Channel	3 Channel	Remote Collection	Batch	Telemed*	Dedicated Computer
			ECG Volume: 3,800/month			
Total cost	21,075.92	16,545.92	17,445.86	17,255.08	19,080.00	17,431.50
Cost/ECG	5.54629	4.35419	4.59104	4.54081	5.02105	4.58724
Difference/ECG	0.00	−1.19211	−0.95525	−1.00548	−0.52524	−0.95906
			ECG Volume: 4,400/month			
Total cost	23,895.56	18,611.56	19,461.28	18,921.58	21,471.00	18,651.00
Cost/ECG	5.43081	4.22990	4.42302	4.30036	4.87977	4.23886
Difference/ECG	0.00	−1.20091	−1.00779	−1.13045	−0.55104	−1.19195
			ECG Volume: 5,000/month			
Total cost	27,526.20	21,488.20	22,287.60	20,573.09	23,862.00	19,893.00
Cost/ECG	5.50524	4.29764	4.45752	4.11462	4.72240	3.97860
Difference/ECG	0.00	−1.20760	−1.04772	−1.39062	−0.73284	−1.52664

* Telemed is a commercial service bureau.
ECG = electrocardiogram.

technical work such as mounting and cutting. Standard safety precautions should be ensured for equipment, fire protection, ventilation and air conditioning. If a magnetic storage medium is used, environmental conditions should be controlled and monitored. Similarly, all necessary electrical installations needed for the support of data processing equipment should meet industry standards and accepted safety practices.

Facilities for recording of electrocardiograms for inpatient and outpatient populations should meet standards for electrical insulation and other safety aspects. Proximity of electrocardiology facilities to the laboratory and the radiology department expedites patient processing, particularly new admissions, with a minimum of patient transportation.

In a single practitioner's office, electrocardiograms can be readily taken in an examining room. Group practitioners performing more than 12 electrocardiograms a day find it convenient to set aside a special area for electrocardiographic recording and processing. This minimizes equipment transfer with attendant damage and allows centralized billing.

Personnel

The method used for electrocardiographic processing plays an important role in determining the personnel requirements. The architectural design of an institution influences the time necessary for an electrocardiographic technician to travel between nursing units.

Ideally, technical and clerical functions should be separate. The extent of technician coverage is, again, a function of electrocardiographic volume and the primary goals of the institution. If an institution uses a three channel recorder,

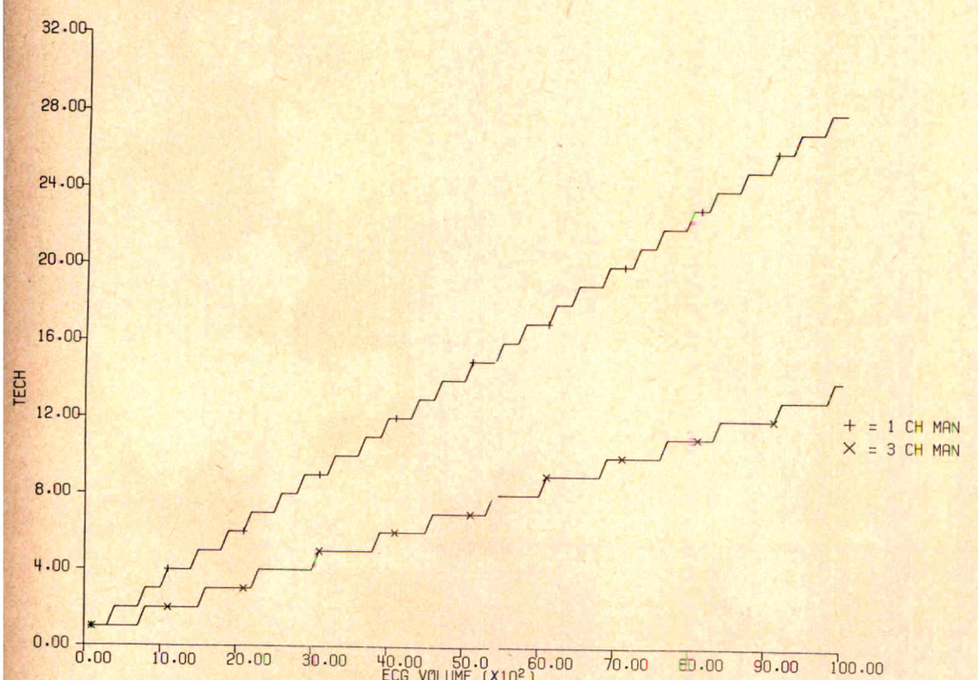

FIGURE 1. Graph showing effects of single and three channel electrocardiographic machines on productivity of technicians. It can be seen that three channel machines consistently save technician time and thus lower costs for personnel. These savings are particularly significant as the volume of electrocardiograms increases. CH = channel; ECG = electrocardiographic; MAN = manual; TECH = technicians.

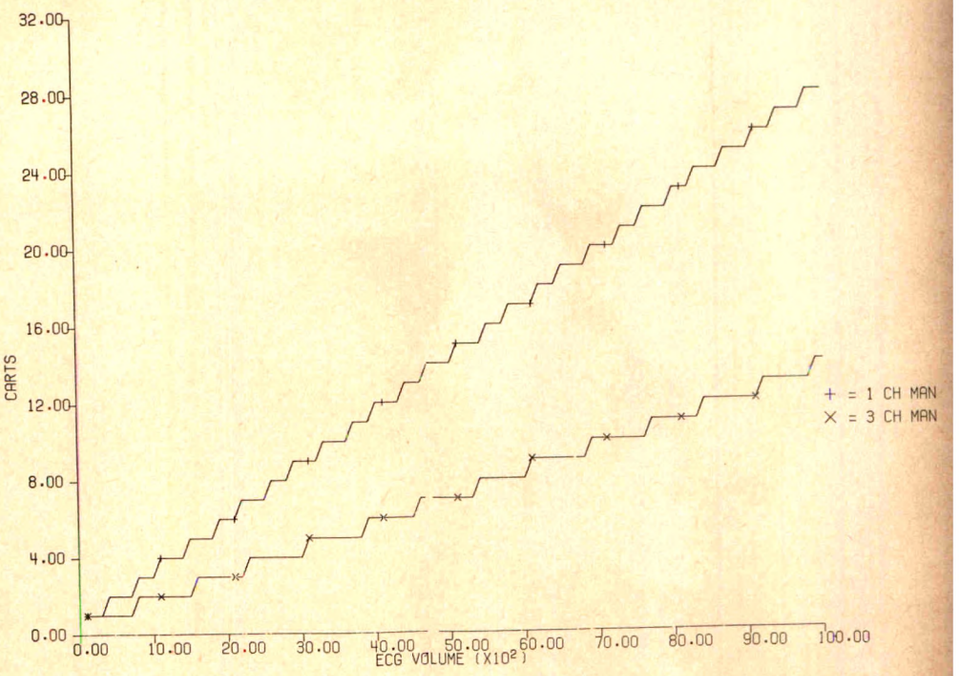

FIGURE 2. Graph showing the number of single channel manual electrocardiographic carts needed to produce tracings at specific volumes versus three channel manual electrocardiographic carts. The use of three channel carts reduces the number of carts needed per 1,000 electrocardiograms. However, three channel carts currently cost six times as much as single channel carts.

trained personnel are needed at all times because the chances of technical errors and equipment breakdown are greater when the equipment is operated by untrained personnel. On the other hand, for institutions using single channel carts, trained nurses, paramedical personnel or house officers may provide adequate service.

It is difficult to determine rigid operational guidelines for electrocardiographic data acquisition because manpower requirements are determined by volume as well as equipment characteristics.

Equipment

For a detailed discussion of the costs and benefits of single channel versus three channel electrocardiographic recorders in various settings, the reader is referred to the "Method for Electrocardiographic Recording" section.

Simulation of Costs

To determine which methods of electrocardiographic acquisition are likely to be cost-effective for a given institution, a computerized simulation can be used. Presented here is information about a simulation program developed by one member of this Task Force (D.R.) to measure alternatives such as single channel versus three channel carts per volume of electrocardiograms to show cost-benefit break points.

The computerized simulation uses cost data obtained from salary and equipment cost records and productivity data obtained from measured performance in situations similar to that of the method to be simulated.

To simulate alternatives properly, two types of items were identified. First, a variable function item has a volume-dependent cost function, which is linear over fixed regions of volume and may have discrete steps associated with particular volumes called break points. An example is an electrocardiographic service bureau with an initial fixed charge, no incremental costs and decreased costs at greater volumes.

The second type is a fixed productivity, fixed cost item. Once the fixed productivity of this item is exceeded, it is assumed that another must be acquired to handle the increased volume. Electrocardiographic carts fall into this category.

Examples of output from the simulation program are given in Table XVII and Figures 1 and 2. These tables compare six alternative methods of providing electrocardiographic support at three selected volume levels and show the calculation of the costs associated with these methods.

Conclusions

1. On the basis of the limited data available to this Task Force, some guidelines for evaluation of costs and cost-effectiveness were developed. However, a more comprehensive study of costs is needed before any firm conclusions on cost-effectiveness can be reached because of hidden costs and other elements that must be identified.

2. Before a new processing system is installed, cost analysis of all available options should be conducted to assure that the new process is the least costly approach to providing the desired service. Costs for each system must be determined individually to take into account institutional and geographic factors.

3. Cost is not the only factor to be considered. Less tangible benefits of computerization may also prove to be determinants.

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Task Force VI: Future Directions in Electrocardiography

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Body Surface Mapping

Purpose: Isopotential body surface maps are used to provide a complete picture of the body surface effects of the currents from the heart. The potential distributions are represented by contour lines of equal potential, and each distribution is displayed instant by instant throughout activation or recovery, or both. Body surface maps do not require the assumption of an equivalent dipole or any other equivalent generator model.

At present, body surface maps provide a standard for testing and comparing lead systems in regard to their ability to reproduce accurately all available body surface electrocardiographic information. Another use is the evaluation of conditions that produce localized changes in the ventricle (ischemia), conditions with the simultaneous presence of prominent repolarization and depolarization potentials (ventricular extrasystoles) and conditions with anomalous sites of excitation (Wolff-Parkinson-White syndrome).

Current status: In 1889 Augustus Waller[1] recorded 10 to 20 electrocardiograms from the surface of the human body and plotted the amplitude on a representation of the human chest. Thereby, body surface mapping was historically the first method used in human electrocardiography. The potential distribution he showed appeared as if a dipole had been located in the chest. Thus, the dipole model of cardiac electrical activity as interpreted from body surface recordings had a major influence on electrocardiographic recording and interpretation for more than 50 years. Since the equivalent dipole can be represented by a vector, three leads are sufficient to define the "heart vector" so as to represent the *equivalent* effect of all the heart currents at any instant of time. However, it was shown[2] that when potential distributions were recorded over extensive areas of the chest, results could not be accounted for on an equivalent dipole basis. In 1963 Taccardi[3] described the sequence of body surface potential distributions during ventricular excitation in normal human subjects and interpreted them physiologically to indicate that a more complex electrical model of the heart was required to account for body surface potential patterns. Since then, extensive studies have confirmed and extended the application of body surface maps in patients. These studies have shown that at some instants the body surface distributions are simple and at other times complex, during both activation and repolarization. Thus, isopotential body surface mapping has provided a stimulus to extend the interpretation of electrocardiograms to one of predicting selective electrical events within the heart, rather than considering only overall equivalent effects.

The technique usually consists of recording in excess of 100 electrocardiographic leads distributed over the entire chest.[4] Recording and data processing are done with the aid of computers, and the entire procedure can be carried out by trained technicians.

The analysis of maps at present is primarily descriptive, as with most conventional electrocardiographic and vectorcardiographic methods. However, quantitative comparisons have been made between normal patients and patients with inferior infarction.[5] Estimates have been made of left ventricular muscle mass and compared with angiographic estimates.[6]

Detailed analysis of maps recorded with more than 100 electrocardiographic leads has shown that for most conditions approximately 24 to 32 leads should provide excellent coverage of the total body surface.[7] This represents a modest increase as compared with the number of leads used to record conventional electrocardiograms and vectorcardiograms but not so many as to be excessively cumbersome. The use of this type of "limited lead" recording system involves the initial recording from approximately 30 leads, and the potentials for all body surface positions are derived from the originally recorded waveforms.

Body surface maps have been used primarily for research purposes; however, there has been preliminary clinical application in the following areas: localization and sizing of myocardial infarcts, detection of areas of ischemia (especially those apparent only with exercise), localization of ectopic foci, and differentiation of aberrant supraventricular conduction from ventricular origin.

Future development: *The principal needs are to* (1) refine the recording and data processing techniques, (2) extend the qualitative interpretation criteria, and (3) develop quantitative models for representing cardiac electric activity from body surface maps. Refinement of the recording techniques to the best number of leads, rapid data processing procedures with small computers, and display of the potential distribution on movie film are needed to make the maps readily available and easily viewed by the physician. The techniques for data presentation to facilitate the review of maps will be important. Especially promising is the use of QRS, T and QRS-T iso-area body surface maps, as proposed by Abildskov et al.[8]

The clinical use of body surface maps is limited at present to qualitative interpretation, which is basically the responsibility of the physician. This will be the main

approach required for some time. Ideally, the physician would be able to interpret events in the heart physiologically, in terms of the heart itself. Consequently, the use of body surface maps has highlighted the importance of developing a generally accepted representation or model of the electric activity of the total heart. At present the isochrome has been used for activation.[9,10] However, this representation cannot be used for the S-T segment and T wave, and other representations must be developed.[11] The representation of cardiac electric activity, as derived from body surface maps, should provide an important clinical tool for extending conventional electrocardiography for the goals noted. In essence, the recording of body surface maps will provide the basis for future research on the "inverse" electrocardiographic problem.[12]

An important immediate application is the use of limited lead systems to record body surface maps during ischemia induced by exercise or pacing. It is already apparent that body surface maps may provide an important way to correlate localized cardiac ischemia with the results of other techniques, such as myocardial imaging and echocardiography. Diagnosis of myocardial infarction that is equivocal or not apparent in conventional electrocardiograms can be facilitated with body surface maps.

Body surface maps should be useful in the study of repolarization to determine the genesis of the normal T wave, to explore further the complex repolarization potential distributions in some abnormal conditions, and to determine the patterns that allow differentiation of minor S-T segment elevations in normal patients from such elevations in patients with ischemic disease.

Body surface maps should provide an improved way to localize more accurately the origin of anomalous sites of excitation such as those that occur in Wolff-Parkinson-White syndrome, extrasystoles and ventricular tachycardia.

Direct Cardiac Mapping—Recording of Potentials Directly From the Heart

Purpose: Cardiac mapping is a method whereby potentials recorded directly from the heart are spatially depicted as a function of time in an integrated manner. The location of recording electrodes (epicardial, intramural or endocardial) and the recording mode used (unipolar versus bipolar), as well as the method of display (isopotential versus isochrone maps), depend upon the problem under consideration.

Current status: Accepted clinical applications have empirically resulted in the almost exclusive use of isochrone maps to depict sequences of activation. The surface activation of the human heart was first reported by Barker et al.[13] in 1930 using the technique of epicardial mapping reported earlier by Lewis and Rothschild.[14] The most elaborate studies were obtained by Durrer et al.[10] and Brusca and Rosettan[15] with in vitro methods using revived human hearts in the adult and the fetus, respectively.

The most successful application of direct cardiac mapping has been in the localization of accessory pathways associated with the Wolff-Parkinson-White syndrome, as first demonstrated by Durrer and Roos[16] in 1967. Experience to date has attested to the value of surgical interruption of the accessory pathway in managing selected patients with life-threatening or medically refractory arrhythmias associated with the preexcitation syndrome. The ability to map the sequence of atrial and ventricular activation is of pivotal significance in the new frontier of electrophysiologic surgery.[17,18]

Endocardial mapping has been used to delineate the anatomic course of the His bundle during open heart surgery to avoid injury to this structure during corrective procedures in *patients with congenital heart disease.*[19] More recently, cardiac mapping has been used to identify the site of rhythm disturbances in patients with ventricular arrhythmias refractory to medical therapy.[20] Similarly, atrial mapping has been used to define the origin of rhythm disturbances in the atria for purposes of surgical ablation.[21]

Another clinical application of cardiac mapping has been to identify areas of myocardial ischemia or infarction for purposes of revascularization or to define margins for surgical resection in the treatment of ischemic heart disease.[22,23]

Future development: *Repolarization potentials,* simultaneously acquired from many cardiac sites, can be displayed as isopotential distributions to identify and localize regions of ischemia. Problems with local injury induced by electrodes must be overcome, as well as alterations introduced by exposure to air and temperature change. Combined with recordings obtained during depolarization, this type of analysis applied to arrhythmias should advance our understanding of the underlying mechanisms and should refine the technique of localizing sites of arrhythmia for purposes of surgical ablation. This development will utilize simultaneous recording sites and on-line computer analysis. Coupled with this will be the requirement that further refinement be made in the techniques available to reproducibly precipitate arrhythmias that are not present spontaneously.

Another application of cardiac mapping will be the correlation of potentials recorded directly from the heart with body surface potentials and cardiac anatomy. Currently accepted electrocardiographic diagnoses such as hemiblock and incomplete bundle branch block are based primarily on a model of abnormality in the specialized ventricular conduction system. Data from carefully constructed activation studies obtained during surgery in such patients, correlated with the associated anatomic and pathologic features of the heart, might explain the abnormal electrocardiogram in these entities and indicate the possible role of myocardial factors.

Intracardiac Electrocardiography

Purpose: The technique of intracardiac electrocardiography involves insertion, under local anesthesia, of one or more multipolar catheter electrodes into a pe-

ripheral vein. The catheter electrode is advanced under fluoroscopic guidance to various positions in the heart. The purpose of such a procedure is to record endocardial activity generated from areas of the atria, ventricles and portions of the specialized conduction system such as the His bundle,[24] right and left bundle branches, and, possibly in the future, from the sinus and atrioventricular (A-V) nodes. In addition, several of these sites can be selectively stimulated[25] with electrical impulses delivered from the catheter electrode.

Current status: Careful assessment of the surface electrocardiogram eliminates the clinical need for intracardiac electrocardiography in many instances. *However, intracardiac electrocardiography may be clinically useful in the following situations:*

1. To measure conduction times and determine refractory periods to establish the presence of normal or abnormal electrophysiologic properties.[26] Such measurements may be useful in evaluating a patient with unexplained syncope, bradyarrhythmia or chronic A-V block to establish the presence and site of the conduction disturbance. The rationale for such an evaluation is based on the generally accepted observation that the presence of conduction delay in the His-Purkinje system carries a worse prognosis. Several points should be stressed. First, conduction disturbances may be labile, so a patient may have a normal H-V (His bundle deflection to onset of ventricular depolarization) interval and still have trifascicular disease with intermittent His-Purkinje block on other occasions.[27] Also, the clinical significance of a prolonged H-V interval has not yet been entirely established.[28]

2. Determination of sinus nodal conduction times[29] *and response to overdrive stimulation.*[30] Estimation of sinus nodal conduction time, determined by the response of the sinus node to premature atrial stimulation, assumes that the rate of sinus nodal discharge is not altered by premature stimulation, that the entire sinus node is totally discharged and "reset" by premature stimulation, and that the conduction time into the sinus node from various atrial sites equals the conduction time out of the sinus node. In fact, such assumptions are probably often incorrect, and determination of sinus nodal conduction time at present must be considered unreliable. Determination of the response of the sinus node to overdrive suppression, as a measure of sinus nodal automaticity, is plagued by a large percent of false negative responses. Patients with documented sinus nodal dysfunction may have a normal response to overdrive stimulation. However, a positive response usually indicates sinus nodal dysfunction.

3. Differentiation of aberrant supraventricular conduction from ventricular origin of the QRS complex. His bundle electrocardiography may be extremely useful for this purpose. The presence of an H-V interval equal to or longer than the H-V interval occurring normally during sinus rhythm establishes a supraventricular origin. A shortened H-V interval indicates the presence of ventricular origin[41] or conduction over an accessory pathway, bypassing normal A-V conduction.[32,33]

4. Determination of the sequence of activation to establish sites of impulse formation or pathways of conduction. Determination of the sequence of activation of the atria or ventricles may be useful in mapping the pathways involved in a tachycardia, such as those reciprocating tachycardias utilizing the accessory pathway in patients with the Wolff-Parkinson-White syndrome,[34–36] and possibly in some patients with ventricular tachycardias.

5. Determination of mechanisms of tachycardia.[37,38] The clinical determination of the mechanism of a tachycardia by the extrastimulus technique is based on the premise that a tachycardia that can be initiated or terminated by one or more premature stimuli is probably due to reentrant excitation, whereas a tachycardia that can be captured or "reset" but not initiated or terminated by pacing stimuli is very probably automatic in origin. Such an approach can be used to investigate mechanisms generating various tachycardias. However, it is important to note that under certain experimental conditions, automaticity can be triggered in isolated preparations.[39,40] This observation raises questions whether the response to premature stimulation can be used to differentiate reentry from automaticity.

6. Evaluation of the effects of drugs. The effect of various drugs can be established in patients at the time of an electrophysiologic evaluation, particularly in patients with tachycardias that can be repeatedly initiated by premature stimulation. After electrophysiologic measurements are obtained under controlled conditions, a drug can be administered to determine whether the drug prevents reinitiation of tachycardia as well as the mechanism by which this occurs. The ability or failure to initiate a tachycardia after drug administration may not necessarily correlate with the spontaneous development of tachycardia in some patients. Drugs may also help to suppress premature complexes that initiate a tachycardia, an event that may not be apparent during the limited time of an electrophysiologic evaluation.

Future development: Future applications of intracardiac electrocardiography will include refinement of its present uses. For example, newer techniques may be developed to evaluate sinus nodal function more accurately. Exploration of the left ventricular endocardium may reveal information regarding ventricular arrhythmias in addition to that obtained by exploration of the right ventricular endocardium. Specifically, areas of delayed conduction or continuous electrical activity may be found in some patients with ventricular arrhythmias.

Intracardiac electrocardiography may be combined with echocardiography or myocardial imaging to develop electroanatomic correlations. Such approaches may be useful to establish new indexes for identification of patients at high risk for sudden death due to A-V block or ventricular fibrillation. It may be that H-V prolongation correlated with one type of anatomic substrate may carry a different prognostic implication from H-V prolongation correlated with a different substrate. Electroanatomic correlations may be useful

in understanding the pathogenesis of some arrhythmias. Finally, intracardiac electrocardiography may be combined with methods for producing localized destruction of tissue permitting localized areas of automaticity or reentrant pathways to be destroyed in a manner similar to that which is done at surgery.

Continuous Electrocardiographic Monitoring

Purpose: Continuous electrocardiographic monitoring allows the detection of changes in the electrocardiogram, such as alterations in the rate and rhythm, conduction and ventricular repolarization as manifested in the ST-T waves. In the hospital this is accomplished with bedside recorders, telemetry, or portable magnetic tape recorders. Portable recorders are used for outpatients. Telemetry is used by rescue units dispatched to victims of cardiac arrest outside the hospital and in rehabilitation programs.

Current status. *In the hospital,* it is standard practice to monitor continuously the electrocardiogram of patients who have had or are at high risk for the development of arrhythmias, such as patients who have acute myocardial infarction, have undergone major surgery or have a critical illness, digitalis intoxication or conduction system disease. Continuous monitoring has been the basis for the development of coronary care units, which have probably reduced in-hospital mortality from myocardial infarction by about 50 percent.[41–43] Telemetry is used mainly in progressive care units where patients can walk. Some computer programs are available for automatic detection, diagnosis and quantification of arrhythmias, but reliance is primarily placed on human surveillance of the continuous recording and on simple alarms based on detection of rate changes. This latter approach fails to detect some transient arrhythmias.

Outpatient monitoring techniques at present allow reasonably reliable detection and categorization of disturbances in rhythm over a 24-hour period using human inspection of the graphic recordings. Detecting arrhythmias in this manner may explain the origin of symptoms, anticipate potentially fatal disorders of rhythm and guide therapy. Recent awareness of the magnitude of the problem of sudden death from arrhythmias[44] has stimulated interest in long-term monitoring to control arrhythmias and identify patients at risk from lethal arrhythmias. Present drawbacks of the techniques include limited capacity for storage of information (limited monitoring period), high cost, unreliable information related to the ST-T wave, and crude, costly and fallible methods for the retrieval and analysis of information.

Future development: *Monitoring in the hospital* could be improved by computer-assisted programs for automatic arrhythmia detection and diagnosis. Some programs have been developed but are not yet validated as to accuracy and reliability. In addition, programmed therapeutic intervention could be instituted. Also, greater capacity for receiving and storing data would allow the recording of more leads and offer some of the advantages of body surface mapping.

For monitoring of outpatients, the present clinical and investigational uses would be facilitated by technical improvements. Methods for data storage other than magnetic tape should be explored. The use of a microprocessor or other large scale integration components might allow some data reduction such as coding or simplification of the wave forms before storage or selection of data for storage. Such a method might prolong the monitoring period and reduce the size of the recorders.

It is likely that developments will enable computer technology to replace or improve current methods of data processing and analysis. It is also conceivable that technologic improvements might lead to the development of implantable permanent monitors of cardiac rhythm to be used in certain categories of patients. Such permanent monitoring would have investigational value, and might be clinically useful if combined with some form of alarm system, some method of programmed therapeutic intervention or some method of transmitting the information to a responsive medical facility.

Signal-Averaging Techniques

Purpose: Signal averaging is a method to improve signal-to-noise ratio applicable to recurrent signals if the noise is "random," that is, not synchronous with the signal. In conjunction with other methods of noise reduction, signal averaging can detect cardiac signals of a few microvolts.

Current status: With this method, potentials generated by the His bundle and bundle branches are detectable at the body surface.[45–54] The duration of the His-Purkinje wave form corresponds to the H-V interval recorded by the catheter technique.

Signal averaging has also been applied to improve resolution of potentials that are detectable by standard recording techniques. Examples of such application include the recording of fetal electrocardiograms[55] as well as of P waves[56,57] and of ST-T waves during exercise. In the last instance, the problem entails reduction of a high noise level introduced by exercise.

Future development: The main impediment to consistent reliable recording of the His-Purjinke wave form is superimposition of atrial potentials when A-V nodal conduction is relatively rapid (P-R interval near the lower limits of normal).[52] Future development will probably require a means of prolonging A-V nodal conduction during the period of recording because filtering techniques have failed to attenuate atrial potentials selectively. In some subjects, skeletal muscle potentials may interfere. Recording His-Purkinje wave forms would allow not only the temporal analysis (H-V time) now provided by the electrode catheter technique but also vectoral analysis. Abnormalities of the His-Purkinje wave form might aid in the earlier detection of conduction system disease, the anticipation of heart block and the differentiation of conduction system disease from other causes of electrocardiographic abnormalities.

The application of signal averaging to ST-T waves or the T-P segment might help to detect delayed activation of diseased ventricular myocardium. Delayed activation potentials might serve as a portent of serious ventricular arrhythmias, a guide to antiarrhythmic therapy, a diagnostic aid in detecting heart disease or a means of differentiating between reentrant and automatic ectopic beats.

The application of signal averaging to intracardiac recordings may enable direct detection of potentials from the sinus node, A-V node, bundle branches, and accessory pathways, or delayed activation potentials of diseased myocardium.[54]

Conventional Electrocardiography

Purpose: The development of conventional electrocardiography has been largely empirical. For example, "significant" Q waves in leads II, III and aVF are taken to imply inferior infarction, not because the mechanism is thoroughly understood but because a significant correlation has been established between the occurrence of Q waves before death and the presence of lesions after death.

Current status: *The specificity and sensitivity of various diagnostic criteria* as interpreted by the electrocardiographer have been extensively evaluated. These studies have shown that the electrocardiogram is diagnostically useful, but the performance is quantitatively limited. For example, a commonly used method for diagnosis of left ventricular hypertrophy has a specificity rate of 97 percent and a sensitivity rate of 60 percent.[58] On the other hand, quantitation of left ventricular mass with various electrocardiographic criteria gave large standard errors of the estimate.[59] Because conventional electrocardiographic analysis is largely empirical, or model-independent, and based upon wave form analysis the computer should be well suited for this task.

The development of computer programs to date has been largely heuristic. Electrocardiograms are classified according to the electrocardiographer's present and past ideas about the meaning of surface electrocardiographic signals. Such programs are usually an attempt to emulate the electrocardiographer. This approach has recently been reviewed by Caceres.[60] A different approach has been taken by Pipberger et al.[61] and Kornreich and Brisme,[62] who performed multivariate analysis of three orthogonal leads and an unconventional lead group, respectively. The development of these programs has been guided by the use of electrocardiogram-independent data.

Future development: *Conventional electrocardiographic studies in the immediate future should be directed toward computer processing.* It is also possible that this may improve the diagnostic performance of the electrocardiogram. Validation of computer program performance should be done using an electrocardiogram-independent objective method. This involves development of a data bank for testing programs quickly and accurately using findings obtained at autopsy and angiography, and by other means.

Magnetocardiography

Purpose: Magnetocardiography is the measurement of the weak magnetic field around the torso that is generated by the heart.[63] Recording these fields requires sophisticated equipment and is facilitated by an environment shielded from the earth's and urban electromagnetic fields

Current status and future development: Magnetocardiography seems particularly well suited to the measurements of "currents of injury," which are manifested by S-T and T-P segment shifts in the electrocardiogram. These shifts have been correlated with reduction of the resting membrane potentials and shortening of the action potential in an ischemic region.[64,65] Cohen and Kaufman[66] have recently reinforced this by measurements of direct current magnetic fields during S-T and T-P segments in experimental myocardial infarction.[67]

As pointed out by Fozzard and DasGupta,[67] this is potentially a valuable observation and is worthy of future study. The collaboration of physical and medical scientists in such studies should be fruitful.

Stress Testing

Purpose: The main purpose of stress testing is to increase myocardial oxygen requirements to unmask an impaired ability of the coronary arterial system to increase myocardial blood flow.[68–71] In most clinical situations, this test is performed to confirm or rule out the diagnosis of coronary artery disease. Stress testing is also useful to obtain an indirect assessment of myocardial function in patients with known or suspected valve or primary myocardial disease. It can also be used to detect exercise-induced supraventricular or ventricular arrhythmias and to evaluate the success of antiarrhythmic therapy in suppressing these arrhythmias.

Current status: The stress electrocardiogram can be obtained by treadmill exercise, bicycle ergometry or other exercise techniques such as the two-step test or hand grip. However, the exercise electrocardiogram is only one aspect of the overall clinical information gained from stress testing. An important aspect of stress testing is to assess the patient's exercise tolerance or overall functional capacity. This type of evaluation can be obtained only through the use of graded exercise[69]; therefore, treadmill or bicycle ergometry is the preferred instrument for the clinical stress test. The diagnostic performance of stress testing has deficiencies, in both specificity and sensitivity.[72]

Future development: *Applications of the stress test will most likely remain the same in the future,* although the broad patient information base that can be obtained from such testing will become more widely recognized. For example, the information gained concerning the patient's exercise tolerance or functional capacity may become more useful for making therapeutic decisions. The presence, magnitude and duration of S-T depression, the blood pressure and heart rate responses at the time of onset of limiting symptoms or electrocardio-

graphic abnormalities, and the presence of auscultatory abnormalities after exercise can now be used for this purpose. It is also possible that the severity of underlying coronary artery disease and myocardial dysfunction can be more closely quantified in the future by carefully evaluating these indirect indexes.

Stress testing has already been combined with myocardial imaging techniques to define better the presence and severity of myocardial ischemia and myocardial dysfunction. In the future, body surface mapping techniques, which would allow recordings during dynamic exercise, should also become available.

Overview

Future directions are predicted on the basis of new information learned in the electrophysiologic laboratories, advances in computer technology and the ability to record and process information rapidly. Much of the future work in electrocardiography will be directed toward two principal areas: (1) surface potential electrocardiography, and (2) cardiac conduction and arrhythmias.

Surface potential electrocardiography: *The conventional electrocardiogram may be used as a method for* (1) individual patient and mass screening, (2) monitoring acutely ill patients or patients with cardiac arrhythmias, and (3) long-term monitoring of rhythm disturbances.

The vectorcardiogram, based on the equivalent dipole model, is well recognized as a first approximation of the cardiac sources; it cannot account for the complete body surface potential distribution. However, to date it has been useful as an intermediate step by virtue of certain lead locations not used in scalar electrocardiograms and because of its graphic spatial-temporal display characteristics. It should be noted that the vectorcardiographic leads can also be synthesized from body surface map data.

Body surface potential distributions will be the primary direction of electrocardiography in the future. Recent work indicates that there is considerable information in the body surface potential distribution that is not adequately recorded or spatially or temporally represented in conventional electrocardiograms or vectorcardiograms. Work is in progress and should continue to define the relation between the body surface potentials, the cardiac potentials and the anatomic and functional changes in the heart that result in these potentials. The recording and analysis of multiple thoracic potentials and potential distributions follow from the relation between (1) thoracic potentials and cardiac potentials, and (2) cardiac potentials, cardiac structures and electrophysiologic function.

Basic studies relating surface potentials to cardiac potentials and anatomy will provide a foundation for future electrocardiography. Certain electrographic patterns, although secondary to one mechanism, may actually be due to another. For example, the patterns referred to as hemiblock or bundle branch block frequently represent variations in geometry, asymmetric myocardial hypertrophy, intramural discontinuities or developmental conduction system asymmetry rather than delay in the specialized ventricular conduction system. Computer simulations of cardiac anatomy and electrophysiology will be used to relate quantitatively the body surface potentials to both activation and recovery. Ultimately, inverse models will be used to predict the cardiac mechanisms of surface potentials.

The aim will be to predict a specific structural or functional state resulting in the potential distribution, or to indicate and statistically rank several possible mechanisms, including combinations of abnormalities such as hypertrophy, multisurface infarction and endocardial conduction system disease.

Arrhythmias and cardiac conduction: The mechanisms for clinical tachyarrhythmias may be diverse. Most of these mechanisms are insufficiently defined, with the possible exception of reciprocating tachyarrhythmias utilizing accessory pathways. The present clinical means for determining the electrophysiologic mechanism of arrhythmias are based on the responses of arrhythmias to electrical stimulation. Certain experimental data indicate that the responses of arrhythmias to extrastimuli may not distinguish reentrant mechanisms from certain abnormal automatic mechanisms.

Clarifying the mechanisms of clinical tachyarrhythmia will likely necessitate various means of study, including multiple simultaneous electrode mapping of activation and refractoriness. Recording the activity of critical regions of the conduction system, as well as from atrial and ventricular myocardium and recording activity from diseased regions, should provide information regarding mechanism and origin of tachycardia. Pharmacologic agents with specific effects on conduction or automaticity may be developed and used to distinguish reentrant from automatic arrhythmias. Also, further studies of programmed stimulation in arrhythmias may disclose more specific responses that will help differentiate mechanisms.

Bradyarrhythmias result from failure of pacemaking or conduction in the specialized conducting system. The present means of diagnosis rely on recording the electrocardiogram during bradyarrhythmia. However, such arrhythmias are often intermittent, so methods for assessing function of the conduction system in the interim are desirable. Such direct assessment could entail the detection of activation or recovery potentials of the specialized conducting system and the response to pharmacologic or electrical stress testing.

Many of the projections for the future cited here have been suggested as specific ways to improve the diagnostic and therapeutic usefulness of electrocardiographic recordings from the body surface and directly from the heart. However, several very important problems requiring solution, such as defining the mechanisms of the origin and maintenance of specific arrhythmias in relation to reentry versus automaticity, currently defy specific predictions for the best approach to solutions. These problems point up the need for detailed studies of ionic mechanisms, cell to cell conduction, structural details and extracellular vis à vis intracellular potentials.

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The Practice of Clinical Engineering, edited by Cesar A. Caceres, MD. New York, Academic Press, 1977, 481 pages, $26.50

Pregnancy Hypertension: A Systematic Evaluation of Clinical Diagnostic Criteria, by Emanuel A. Friedman, MD. ScD, and Raymond K. Neff, ScD. Littleton, Massachusetts, PSG Publishing, 1977, 400 pages, $40.00

Pulmonary Pathophysiology: The Essentials, by John B. West. Baltimore, Maryland, Waverly Press, 1977, 227 pages, $9.95

Quality Assurance in Long Term Care, by T. H. Ainsworth, Jr. Germantown, Pennsylvania, 1977, 214 pages, $17.00

Recent Advances in Blood Coagulation, edited by L. Poller. New York, Churchill Livingstone, 1977, 388 pages, $35.00

Respiratory Disease, by D. J. Lane, MD. New York, Appleton-Century-Crofts, 1976, 565 pages

Thrombosis and Urokinase (Proceedings of the Serono Symposia, Volume 9), edited by R. Paoletti and S. Sherry. New York, Academic Press, 1977, 257 pages, $16.00

Trends in Computer-Processed Electrocardiograms, edited by J. H. Van Bemmel and J. L. Willems. Amsterdam, North-Holland Publishing, 1977, 437 pages, $46.95

27th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Anaheim, California **March 6–9, 1978**

President's Page:

Cardiology 1978 at Anaheim—
Welcome to the College's 27th Annual Scientific Session

Dr. Mason

On behalf of the Officers, Membership and Staff of the College, it is my sincere pleasure and great privilege to extend a personal invitation to each of you and your families to join me, my wife Maureen and our two daughters at the world-renowned Anaheim Convention Center this forthcoming March 6–9, 1978 during the College's 27th Annual Scientific Session. The Disneyland Hotel will serve as our Headquarters Hotel. I am delighted to report that the most expansive educational program yet formulated by the College awaits you in beautiful Southern California. I am certain that you will be highly impressed by the superb quality and comprehensive extent, encompassing the spectrum of modern knowledge relating to cardiovascular diseases, of this year's program, which has been prepared in a variety of learning formats, with many innovations, by the Scientific Program Committee with Dr. Anthony N. DeMaria, Chairman, and Dr. Nemat O. Borhani, Co-Chairman. Equally stimulating are the several cultural, social and recreational activities planned by Dr. Eliot Corday, Local Arrangements Chairman, and Mrs. J. Douglas McNair, Hospitality Program Director. Considering the exciting combination of these favorable features, Anaheim 1978 promises to be a memorable event for both physician attendees and their families.

The annual meeting actually begins on March 5 with a new educational offering, a sequence of Mini-Courses on Sunday afternoon and Monday morning. These postgraduate symposia have been designed to provide a basic fund of information in certain major areas in adult and pediatric cardiovascular medicine and surgery. Organized and directed by recognized authorities, the Mini-Courses include Patient Presentations (Dr. Robert O'Rourke), Electrocardiography of Arrhythmias (Dr. Charles Fisch), Echocardiography (Dr. Harvey Feigenbaum), Exercise Testing and Cardiac Rehabilitation (Dr. Albert Kattus), Cardiac Pathology (Dr. William Roberts), Nuclear Cardiology (Dr. Daniel Berman), Hypertension (Dr. Ray Gifford), Conduction System in Children (Dr. Paul Gillette), Cardiovascular Pharmacology (Dr. William Parmley), Acute Myocardial Infarction—1978 (Dr. H. J. C. Swan), Ambulatory Monitoring (Dr. Eliot Corday) and Lipid Disorders (Dr. Robert Levy).

The Opening Plenary Address on Monday afternoon, March 6, presented by Dr. Bernard Lown, will be on "Sudden Cardiac Death—The Major Challenge Confronting Contemporary Cardiology." The Bishop Lectureship will be given by Dr. Rene Favaloro on "Direct Myocardial Revascularization—A Ten Year Journey: Myths and Realities," Tuesday afternoon, March 7. We are also honored that Mr. Norman Cousins, Editor of the *Saturday Review*, will be our Convocation Speaker on Wednesday evening, March 8.

The Core Curriculum of fundamental education in cardiovascular mechanisms, diagnosis and therapy is composed of 10 different sessions to be presented sequentially throughout the 4-day annual scientific session. The following Special Structured Sessions will focus on recent advances in cardiovascular diseases: "Vasodilator Therapy in Heart Failure," "Sudden Death," "Congenital Aortic Stenosis," "Coronary Artery Surgery," "Thrombosis," "Plasma Lipids and Atherosclerosis," "Advances in Drugs in Pediatric Cardiology," "Role of Noninvasive Techniques in Evaluation of Angina Pectoris," "Latest Observations in Cardiovascular Pathology," "Valvular Heart Disease," "Cross-Sectional Echocardiography," "The Coronary Care Unit—1978," "Advances in Cardiac Catheterization," "Nuclear Cardiology—1978," "Pacemakers—1978" and "Results of Multicenter Clinical Trials in Coronary Artery Disease Prevention."

The popular educational format of the Controversies in Cardiology is particularly enticing this year. Expert protagonists and antagonists will debate the still controversial subjects of "Intraaortic Balloon Counterpulsation," "Myocardial Revascularization and Longevity," "Exercise Training Effects on Coronary Disease," "Therapy of Chronic Ventricular Premature Beats," "Exercise Stress Testing in Coronary Disease Detection" and "Porcine Heterograft Valves Versus Mechanical Prostheses."

In addition, opportunities will be afforded for exchange of knowledge and ideas in the 36 small group Meet-The-Experts sessions as well as in the 30 evening Fireside Panels and the 40 Luncheon Panels. Dr. R. Joe Noble will direct the Self Assessment Program, which is to be principally centered on echocardiography throughout our annual scientific meeting. Also available throughout the meeting will be the Industrial Cardiovascular Instruction (ICI) area where Accel audio and video supplement tapes may be reviewed.

This year's scientific program will provide a greater opportunity than ever before for abstract presentations of original investigations in both basic and clinical aspects of cardiovascular diseases. For our 1978 meeting, we received a record number of 1,473 abstracts of

which it will be possible to present the 374 highest graded (approximately 25 percent) during our annual session. The Young Investigator's Award presentations will again be carried out on Wednesday morning, March 8.

We have given special recognition to the advent of preventive cardiology as an integral aspect of the daily activities of every physician involved in cardiovascular patient care. Thus, the theme adopted for this year's program is "Preventive Aspects of Cardiovascular Diseases." Accordingly, throughout our meeting, emphasis will be given to diagnostic and therapeutic modalities in each area of cardiovascular practice and research which are of value in the prevention of clinical heart diseases.

The Hospitality Program is unique in scope and special in unusual events designed to provide cultural experiences and necessary periods of relaxation. Two highlights are particularly noteworthy. On Sunday evening, arrangements have been made for attendees, their families and exhibitors to attend a special opening of Disneyland Park for a "Night at Disneyland." Then on Wednesday, March 8, a unique Costume Design Showing by Edith Head will be presented. In addition to these special events, Mrs. J. Douglas McNair has arranged daily visits to the Sea World in San Diego, San Juan Capistrano and Lion Country Safari, Newport and Laguana Beach Tours with Harbor Cruise, Knott's Berry Farm, Universal Studios and the Movieland Wax Museum. Also secured by Mrs. McNair are a tour of the Norton Simon Museum, a Huntington Library, Art Gallery and Botanical Gardens tour and a variety of special presentations: Transactional Analysis Women Leadership, by Sasha Sherbin; Pictographic Demonstration of Improvements in Color Photography, by Mr. Tim Taylor; Effective Reading—A Lifetime Technique, by Mrs. Carey Roberts; Precious Gems, by Lynette Barnes; and Graphology (handwriting analysis). Furthermore, on Monday and Tuesday evenings, when spouses are attending scientific Fireside Sessions, a Family Bingo program has been planned. The Hospitality Program Committee has also scheduled a Welcoming Brunch on Monday, March 6, to honor the spouses of new members of the College.

Finally, a special welcome is offered to those of you who can join us at the Post-Anaheim Symposium on Clinical Cardiology in Kauai, Hawaii, March 10–12, 1978.

Judging from the intense interest already shown and the outstanding educational and cultural experiences afforded, Anaheim 1978 promises to be the best attended of our annual meetings. I look forward to welcoming each of you to my native state of California for the College's 1978 Scientific Session.

Dean T. Mason, MD, FACC
President 1977–78

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education.

Each continuing education program is directed toward a specific target group including: adult cardiologists (CD), internists (IM), pediatric cardiologists (PDC), and family practitioners (FP). For additional information concerning the programs listed below or for a complete schedule of programs through October 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

FEBRUARY THROUGH APRIL 1978

Feb. 6–8 **Pediatric Cardiology: Clinical-Pathological Correlations (PDC) (IM).** William C. Roberts, MD, FACC, director

Feb. 20–22 **Difficult to Manage Cardiovascular Problems: The Systematic Approach (FP).** Robert S. Eliot, MD, FACC, director

Feb. 27–Mar. 1 **Clinical Decision Making in Coronary Artery Disease (CD) (IM).** Arthur Selzer, MD, FACC, director

Mar. 27–30 **Congestive Heart Failure: A Changing Scene? (CD) (IM).** Charles B. Mullins, MD, FACC, director

Apr. 3–6 **Cardiac Emergencies: Recognition and Therapy (CD) (IM).** Charles E. Rackley, MD, FACC, director

Apr. 10–12 & 13–15 **Adult Echocardiography: Clinical Applications and Recent Advances (CD) (IM).** Pravin M. Shah, MD, FACC, director

Apr. 17–20 **Pediatric Echocardiography (PDC).** Richard A. Meyer, MD, FACC, director

Apr. 24–26 **Exercise Testing: Diagnostic and Physiologic Considerations (CD) (IM).** Keith Cohn, MD, FACC, director

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

JANUARY 1978 THROUGH APRIL 1978

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

JAN. 9–13 — **Ninth Annual Cardiovascular Conference in Snowmass.** John H. K. Vogel, FACC, director and James S. Forrester, FACC and Bruce C. Paton, FACC, co-directors, Snowmass Resort, Snowmass, CO

JAN. 9–13 — **Fundamentals of Echocardiographic Interpretation.** Vincent E. Friedewald, Jr., director, Kauai Surf Hotel, Kauai, HI

JAN. 20–21 — **New Developments in Stress Testing.** Myrvin H. Ellestad, FACC, William H. Allen, FACC and Robert Stuart, co-directors. Memorial Hospital Medical Center of Long Beach, Long Beach, CA

FEB. 3–5 — **Management of Cardiac Diseases—1978.** Robert J. Myerburg, FACC and Agustin Castellanos, FACC, co-directors. Omni International Hotel, Miami, FL

FEB. 23–25 — **Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** John Ross, Jr., FACC, Joel S. Karliner, FACC, Ralph Shabetai, FACC, Kirk L. Peterson, FACC and Allen D. Johnson, FACC, co-directors. Hotel del Coronado, Coronado, CA

MAR. 3–4 — **Complex Problems in Congenital Heart Disease.** Robert M. Sade, FACC and Arno R. Hohn, FACC, co-directors. Kiawah Island Inn, Charleston, SC

MAR. 6–9 — **Twenty-seventh Annual Scientific Session.** Dean T. Mason, FACC, president. Anaheim Convention Center and Disneyland Hotel, Anaheim, CA

MAR. 10–11 — **Post Anaheim, California. Symposium on Clinical Cardiology.** Anthony N. DeMaria, FACC, director. Kauai Surf Hotel, Kauai, HI

MAR. 27–31 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

MAR. 30–APR. 1 — **Contemporary Management of Acute Myocardial Infarction by the Family Physician.** Robert S. Eliot, Chairman and Ernie J. Chaney, Alan D. Forker, Harold Kalman and Thomas Nicholas, program committee. Sarasota Hyatt House, Sarasota, FL

APR. 3–7 — **Consultant's Course in Cardiology.** Michael V. Herman, FACC, director and Simon Dack, FACC, Richard Gorlin, FACC and Louis E. Teicholz, FACC, co-directors. Mount Sinai Medical Center, New York, NY

APR. 3–12 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 12–14 — **Vectorcardiography: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 19–21 — **Echocardiographic Solutions to Clinical Cardiovascular Problems.** Joseph K. Perloff, FACC and John S. Child, FACC, directors. Century Plaza Hotel, Los Angeles, CA

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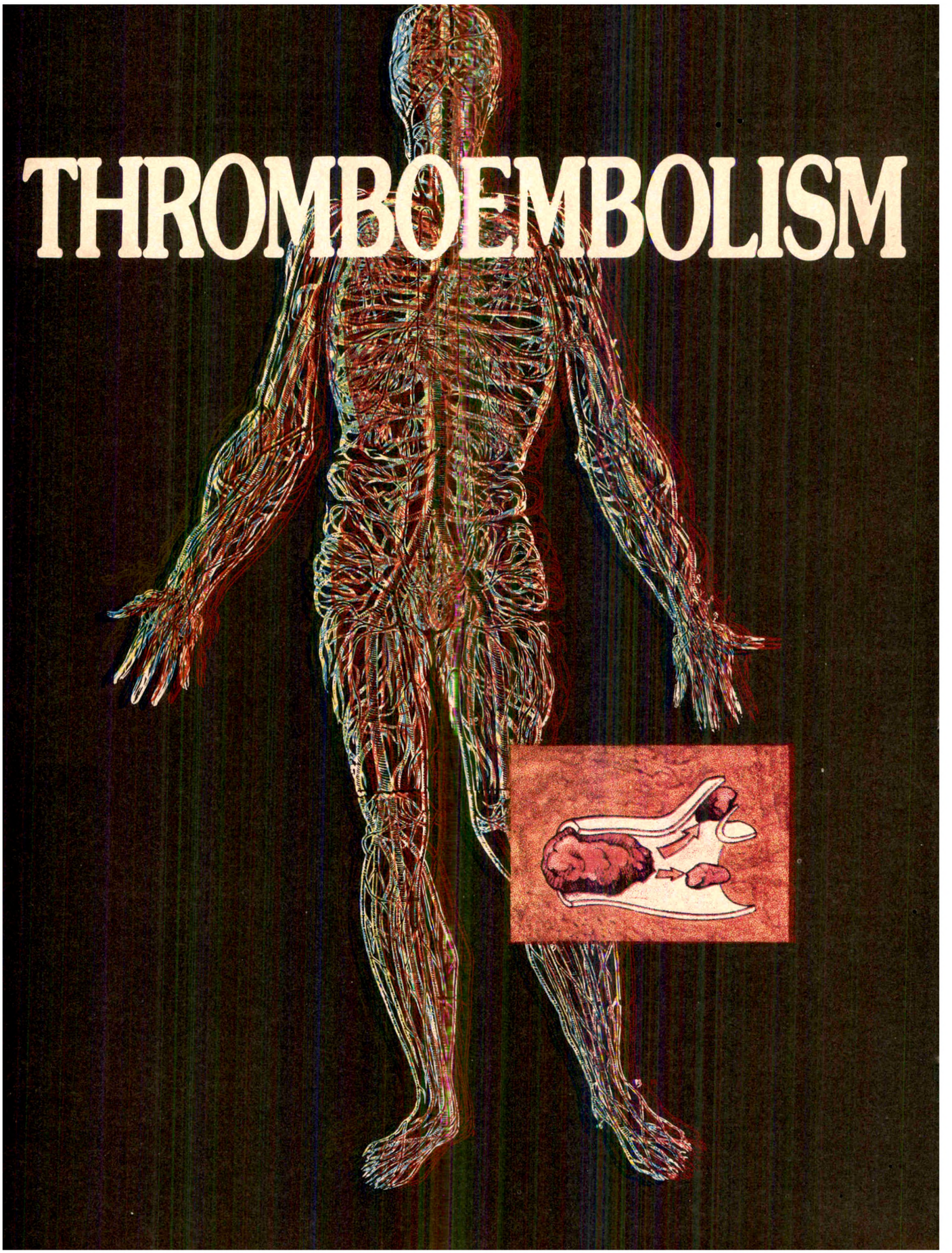
THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DU PONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin* anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

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*Present as crystalline sodium warfarin isopropanol clathrate.

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For the PVD patient, walking can be productive instead of just painful

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Studies† have demonstrated that a program of regular walking exercise can significantly extend the distance and time these patients can walk without claudication. In one study walking exercise of one hour daily has been shown to effect noticeable improvement in a month. After six months, pain-free walking increased to twice that of pre-exercise levels.

Investigators have attributed the improvement to vasodilating effects of exercise, increased venous return and development of the collateral circulation. It is clear that exercise produces a tolerance for more exercise, and a program of regular walking, in the absence of any contraindications, appears to be an appropriate measure in the management of Peripheral Vascular Disease.

The Value of Proper Gait

Patients often compensate for claudication in calf muscles by adopting a shuffling gait. This "shuffling" utilizes calf muscles only minimally.

The diagram on this page illustrates the normal gait—described as "heel-and-toe" walking. Patients who are encouraged to become more conscious of their gait and to walk properly will utilize calf muscles to a greater degree—and maximize the therapeutic effects of a prescribed walking program.

The Role of Arlidin® (nylidrin HCl)

Arlidin improves blood flow by dilating responsive vessels in skeletal muscles. The symptoms of ischemia may therefore be relieved thus encouraging the patient to begin or continue with an appropriate exercise program.

Furthermore, Arlidin maintains mean arterial pressure, thus maximizing delivery of blood to ischemic areas and minimizing the risk of postural hypotension. Its vasodilating effect in skeletal muscles and maintenance of mean arterial pressure make Arlidin an appropriate adjunct to other measures—such as walking—in the management of Peripheral Vascular Disease.*

PROPER HEEL-AND-TOE WALKING

HEEL STRIKE PUSH-OFF HEEL STRIKE

You can obtain a more detailed version of this chart, explaining heel-and-toe walking to patients, from your USV Representative or by writing to Medical Department, USV Laboratories Inc., Tuckahoe, N.Y. 10707.

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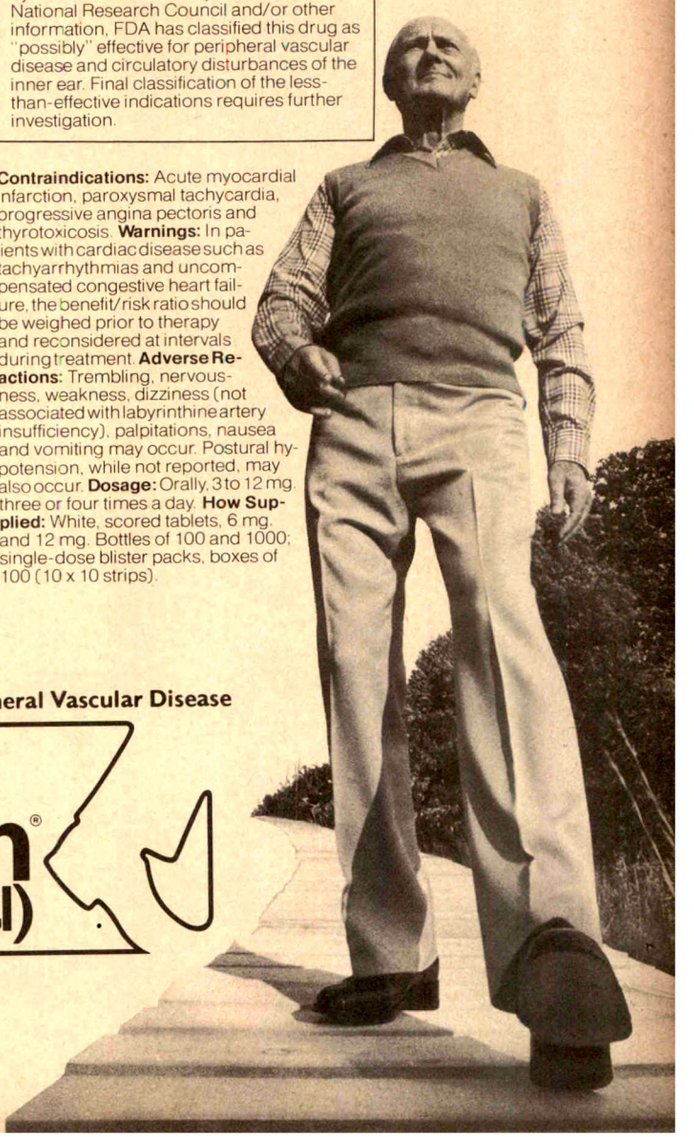
***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).



The new prescription for Peripheral Vascular Disease

Walking & Arlidin® (nylidrin HCl)

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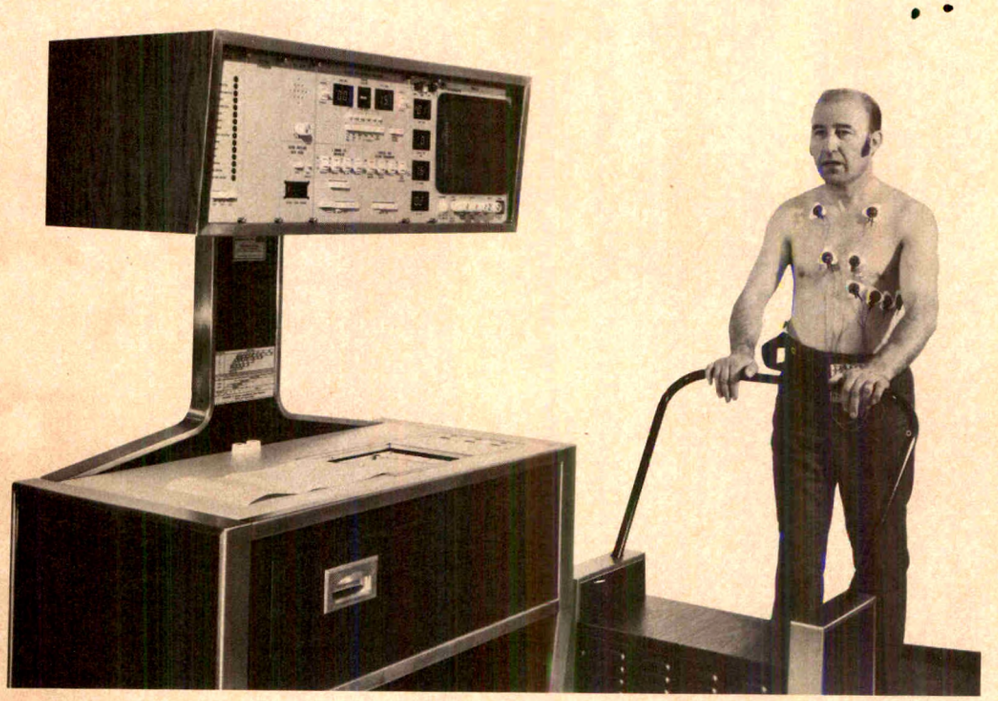

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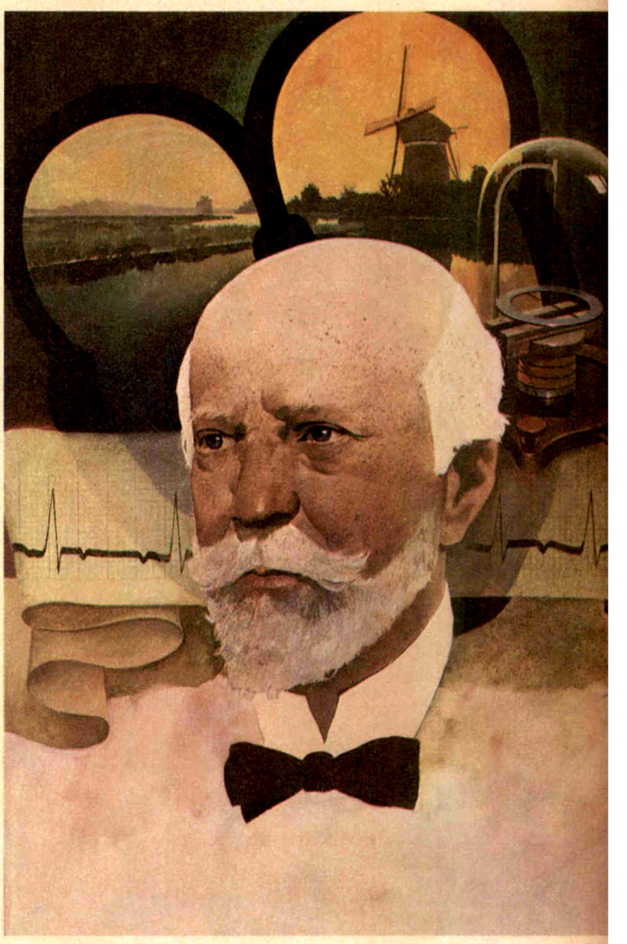

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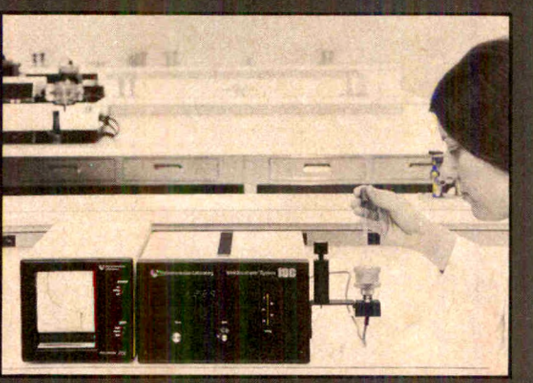
[1]Protasio L. da Luz, M.D. et al., "Pulmonary Edema Related to Changes in Colloid Osmotic and Pulmonary Artery Wedge Pressure in Patients after Acute Myocardial Infarction," *Circulation*, LI (Feb. '75), 350-357.



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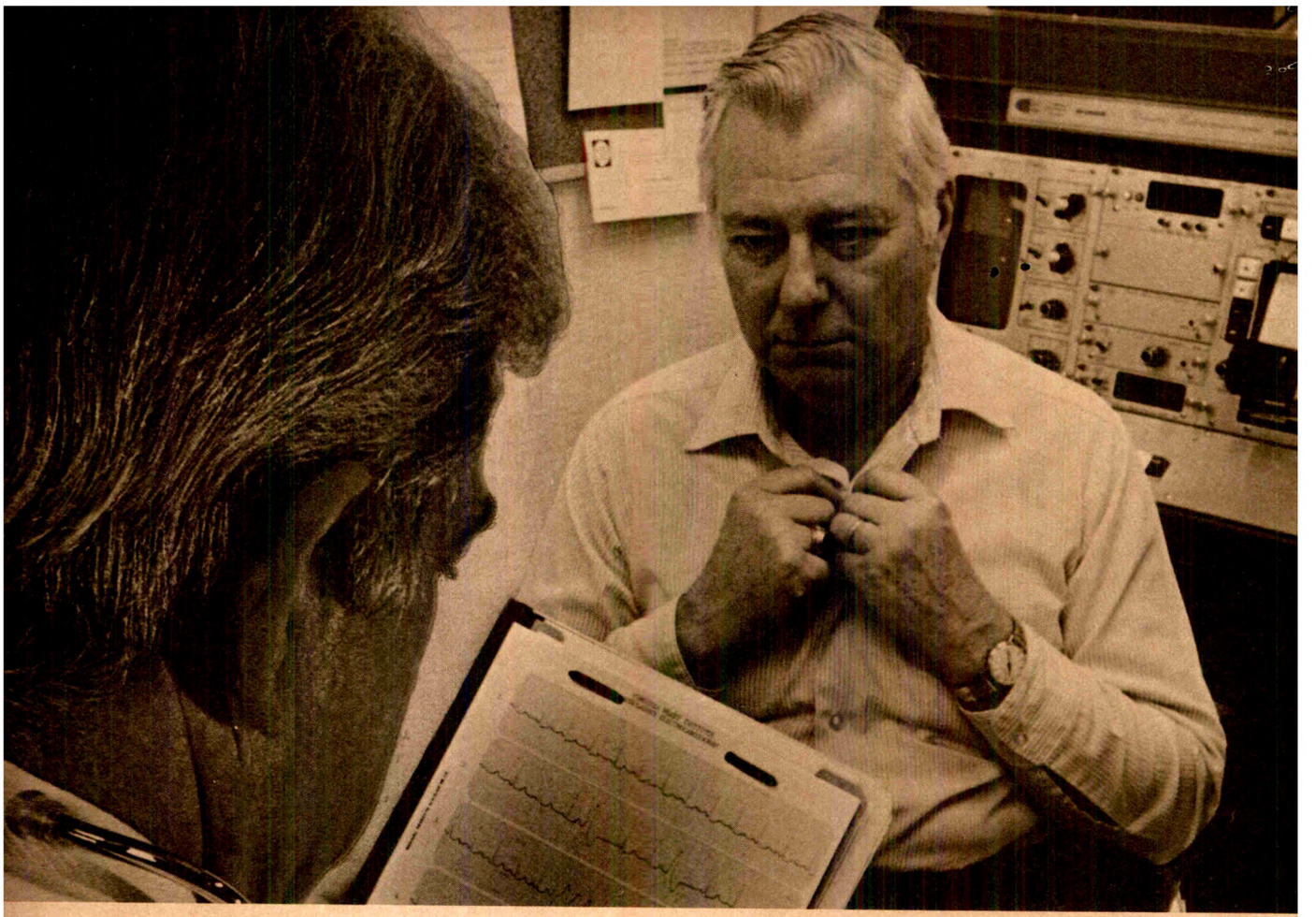

Diagnosis: PVC's
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initial therapy:
quinidine sulfate tablets
at
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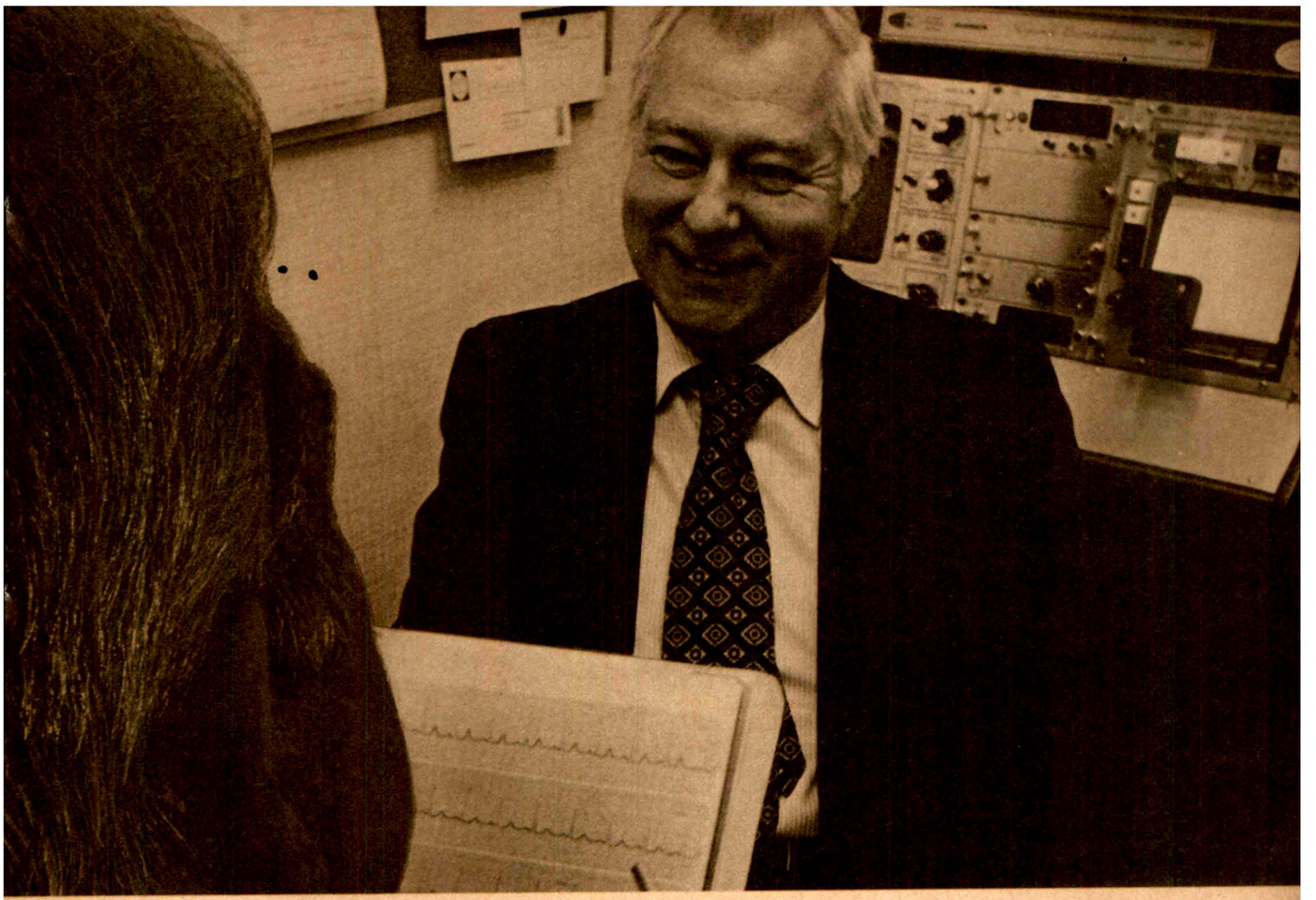
5 p.m.
9 p.m.



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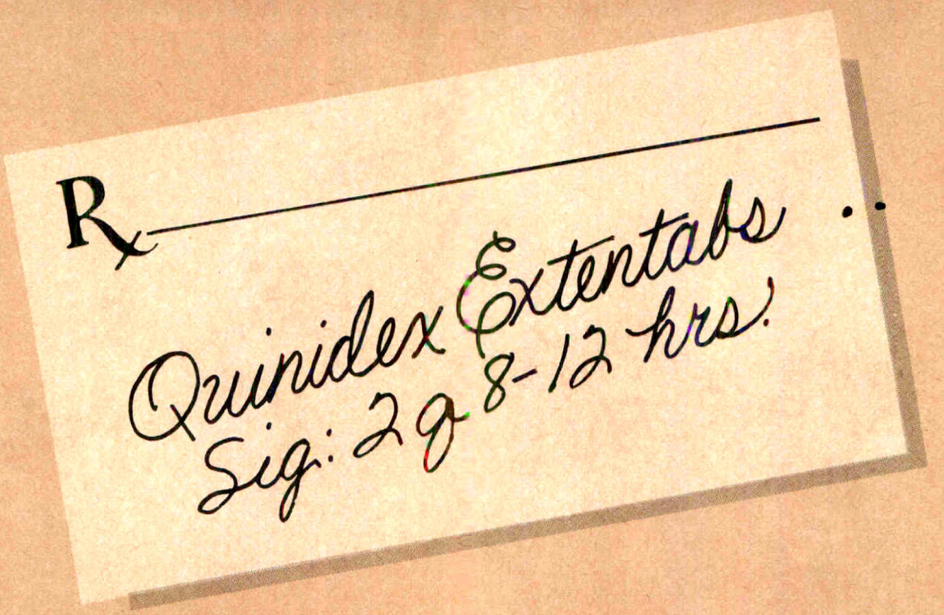

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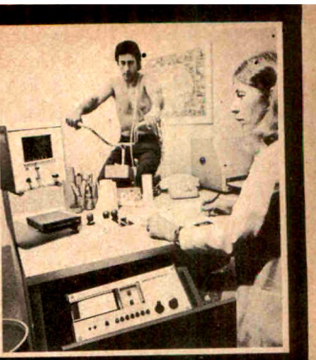

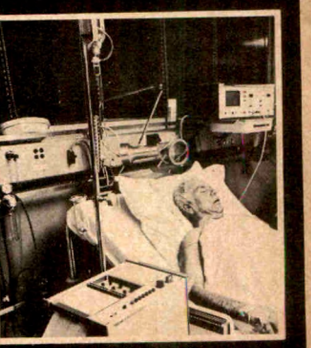

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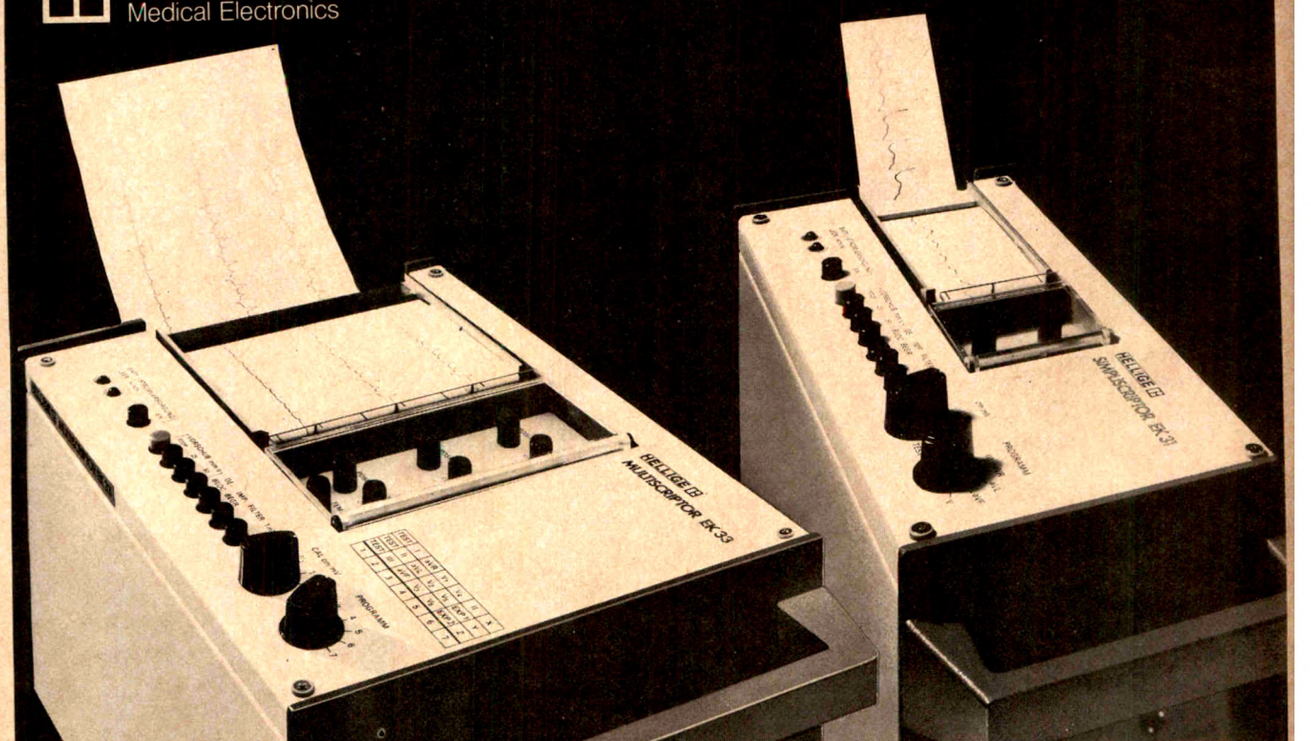

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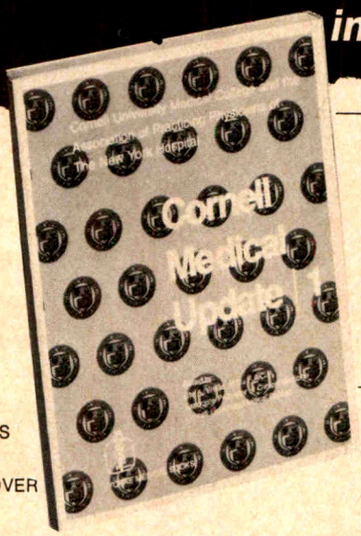

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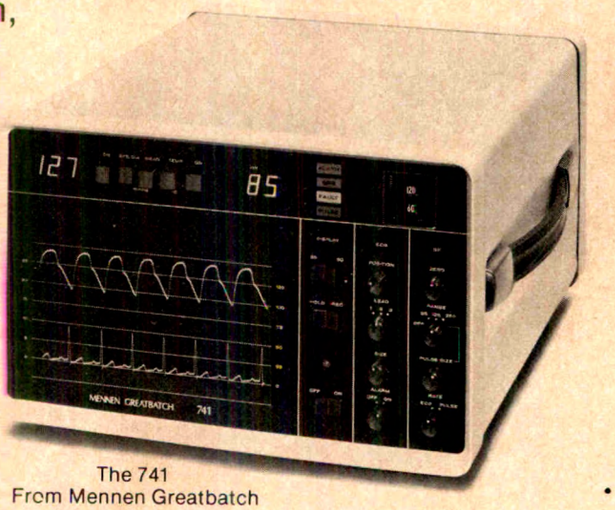

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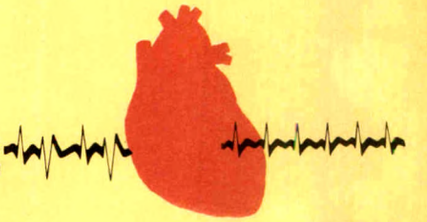
Searle announces...

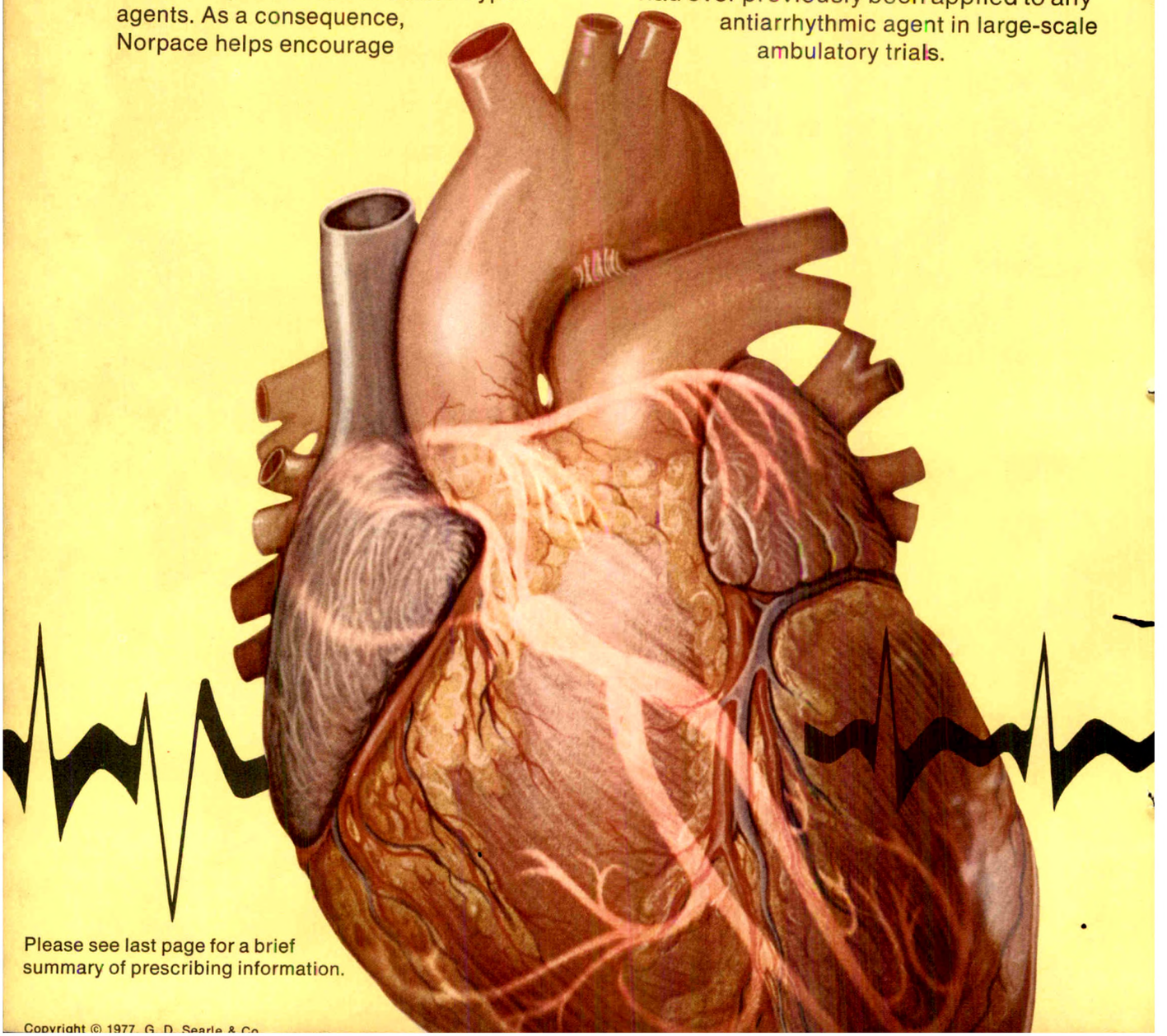
a unique agent for the treatment of specific ventricular cardiac arrhythmias



Introducing
the first antiarrhythmic proved

Norpace (disopyramide phosphate) is a product of Searle Laboratories and the result of many years of research and clinical testing. It satisfies the recognized need for a new oral agent that effectively treats serious ventricular arrhythmias and is relatively safer than available Type I agents. As a consequence, Norpace helps encourage patient compliance and can be prescribed with confidence.

Searle Laboratories will be pleased to provide detailed information on the clinical trials, which used a more sophisticated means of evaluating efficacy than had ever previously been applied to any antiarrhythmic agent in large-scale ambulatory trials.



Please see last page for a brief summary of prescribing information.

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effective by extensive Holter monitoring

Norpace®

(disopyramide phosphate)

as effective as quinidine sulfate for specific ventricular arrhythmias...but with less severe side effects

Norpace efficacy was thoroughly proved and documented

Norpace was clinically evaluated in patients monitored by 9-hour Holter ECGs while receiving placebo (two distinct periods) and Norpace (two distinct periods). Significant reductions in ventricular ectopy were recorded during Norpace therapy. Norpace was also compared with quinidine sulfate (quinidine), a standard antiarrhythmic agent, in patients randomly assigned in double-blind studies, and was shown on the basis of 9-hour Holter monitoring to be as effective as quinidine in reducing ventricular ectopic activity. Finally, in oral acute studies involving 3-hour continuous ECGs, Norpace demonstrated the following: 1) a rapid onset of antiarrhythmic activity following an initial loading dose—achieving therapeutic plasma levels usually within ½ to 3 hours; 2) continued suppression of ectopy as a result of maintenance dosing over the subsequent 3 days; and 3) further suppression of ectopy when dosage was increased in most cases where breakthrough was noted. No currently available antiarrhythmic agent has been subjected to such a rigidly controlled program of study prior to introduction as has Norpace, nor have other antiarrhythmics been evaluated in a controlled comparison with a known standard such as quinidine.

Norpace effectively treats specific ventricular arrhythmias

Norpace is indicated when there is electrocardiographic evidence of premature ventricular contractions (PVCs): unifocal, multifocal, or paired PVCs, or episodes of ventricular tachycardia (VT). Significant reductions in these ventricular arrhythmias have been demonstrated by 9-hour ambulatory ECG recording.

During the clinical trials, efficacy in treating ventricular arrhythmias was proved in patients with primary cardiac arrhythmias or arrhythmias associated with coronary artery disease, and also in patients who were digitalized.

Norpace demonstrated excellent patient tolerance

In a double-blind multicenter clinical study (see next page for details), Norpace was found to have less severe side effects than quinidine sulfate and to be significantly better tolerated. The side effects of Norpace, in contrast with those of quinidine, were generally mild, being primarily anticholinergic in nature and frequently transient.

Norpace demonstrated dose-related plasma levels

Therapeutic levels ranging from 2-4 μg/ml are attained in response to 150 mg q 6 h. Some patients with unusually refractory ventricular arrhythmias have required doses up to 400 mg q 6 h which produced plasma levels in the range of 4-8 μg/ml.

Norpace has minimal effect on hemodynamics

At recommended oral doses, Norpace rarely produces significant alterations of blood pressure. Hemodynamic studies of the intravenous administration of Norpace in patients with coronary artery disease have revealed minimal cardiac depression with approximately a 10% reduction in cardiac output.

SEARLE

from clinical studies...

Norpace®
(disopyramide phosphate)

proved as effective as quinidine sulfate for specific ventricular arrhythmias...

Results of double-blind controlled studies

A double-blind multicenter clinical study, involving five investigators, was conducted to compare the relative effectiveness and safety of Norpace and quinidine sulfate. Prior to qualifying for the study, each patient had antiarrhythmic medication discontinued for at least one week. Nine-hour Holter recordings were then used to establish an admission criterion of at least 60 ectopic beats per hour (PVCs, PACs or combination of the two). All other arrhythmias were excluded except paroxysmal ventricular or atrial tachycardias occurring in conjunction with the above.

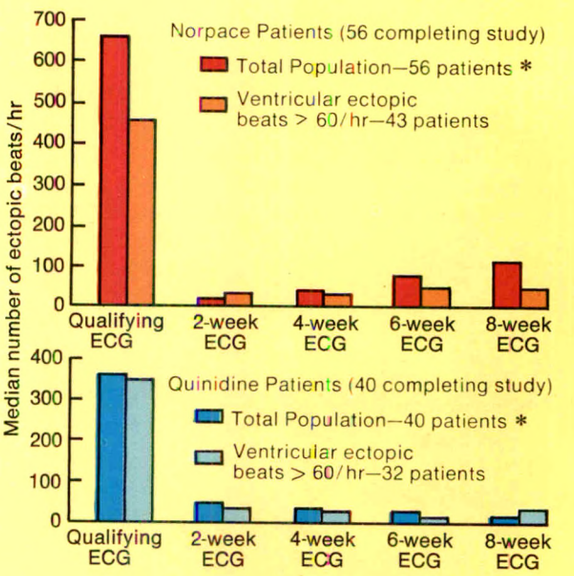
Study protocol

After qualifying, patients were randomly assigned to receive either Norpace (150 mg q 6 h) or matching capsules of quinidine sulfate (325 mg q 6 h). Consultant cardiologists, based on their clinical experience, predicted these dosages to be comparable in effect. Every two weeks during the 8-week course of the study each patient returned to the investigator for a new supply of capsules and a 9-hour Holter recording. The four Holter recordings during therapy plus the qualifying recording provided objective, quantifiable electrocardiographic evidence of patient response to therapy.

Norpace proved comparable to quinidine sulfate in reducing ventricular ectopic beats

Figure 1 presents the relative effectiveness of Norpace and quinidine sulfate in reducing total and ventricular ectopy. It was apparent that both drugs were capable of reducing ectopic activity and maintaining suppression throughout the course of therapy.

Fig 1. Median number of ectopic beats during successive 2-week Holter recordings for Norpace- and quinidine-treated patients.



* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

SEARLE

with less severe side effects

Relative safety of Norpace (disopyramide phosphate) and quinidine sulfate

Reported side effects
The entire study population was analyzed for side effects. The side effects experienced by Norpace patients were usually mild and mainly anticholinergic, including: dry mouth, urinary hesitancy, constipation, blurred vision. The anticholinergic side effects were generally transient.

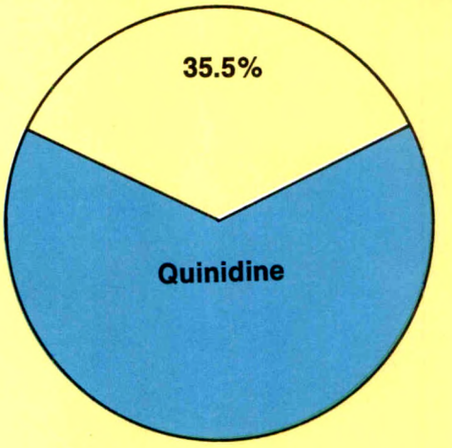
Adverse reactions with quinidine were more serious and affected a greater number of patients. The most common symptoms were: severe diarrhea, cramps, nausea, vomiting, headache, dizziness, blurred vision, fever, chills and diaphoresis.

Reasons for discontinuation of therapy
Twenty-two quinidine patients discontinued therapy because of toxic effects, most of them within the first 2 weeks of treatment. Most of the quinidine sulfate dropouts experienced combinations of gastrointestinal symptoms often accompanied by dizziness and in five cases by a generalized pruritic rash.

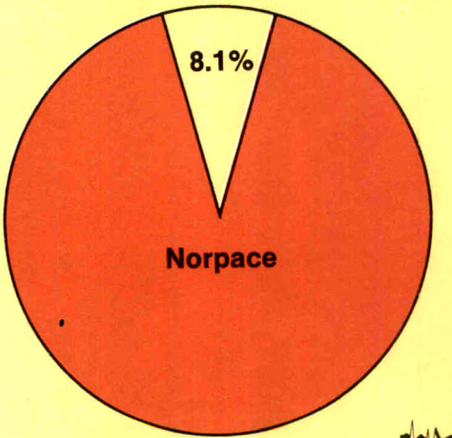
Five Norpace patients dropped out of the study, as a result of the following side effects: nausea and dizziness (2); pains in neck and back (1); urinary complaints in patient with known benign prostatic hypertrophy (1); and persistent paroxysmal ventricular tachycardia (1). (One patient dropped out because of lack of interest.)

Norpace patient group had significantly fewer dropouts due to side effects

Quinidine dropouts in 62 patients



Norpace dropouts in 62 patients



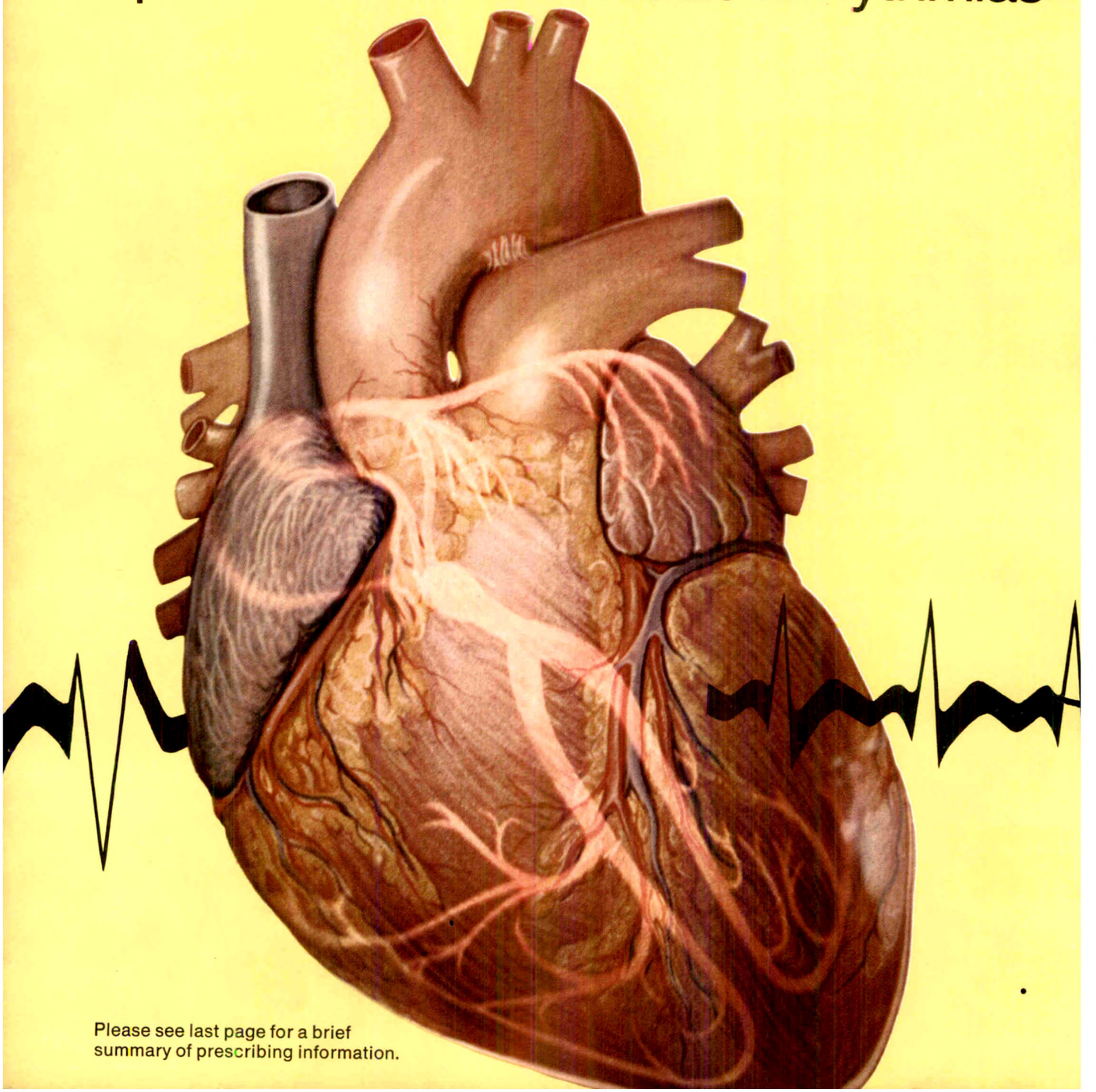
Please see last page for a brief summary of prescribing information.

New from Searle

Norpace®

(disopyramide phosphate)

a unique agent for the treatment of specific ventricular cardiac arrhythmias



Please see last page for a brief summary of prescribing information.

Dosage and administration

Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance.

Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose.

Recommended dosage regimen

Patient type	Loading dose	Maintenance dose
Adult	300 mg	150 mg q 6 h
Adults of smaller stature; or with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation	200 mg	100 mg q 6 h
Adults with severe renal insufficiency C_{cr} less than 40 ml/min	200 mg	100 mg given approximately every half-life (see Note below)

Note: Since Norpace is excreted in the urine, renal insufficiency appreciably extends the half-life of the drug. The chart below provides guidelines to the appropriate Norpace dosage in such patients.

Norpace dosage interval adjustment for renal insufficiency

Creatinine clearance ml/min.	40-15	15-5	5-1
Approximate maintenance dosing interval	q 10 h	q 20 h	q 30 h

- Norpace plasma half-life may also be prolonged in patients with significant liver disease.

Norpace®
(disopyramide phosphate)

- Effective as quinidine sulfate for specific ventricular arrhythmias and significantly better tolerated
- Compatible with digitalis
- Minimal effect on hemodynamics

SEARLE

Norpace®
(disopyramide phosphate)

as effective as quinidine sulfate for specific ventricular arrhythmias... with less severe side effects

SEARLE
NORPACE® CAPSULES
brand of disopyramide phosphate

Before prescribing Norpace, please consult complete prescribing information, a summary of which follows:
Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and non-digitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia, atrial arrhythmias or arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.
Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.
Warnings: Severe hypotension has been observed on rare occasions, primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless it is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may cause cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma or urinary retention, unless adequate overriding measures are taken.
Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.
Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites in milk is up to three times greater than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.
Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.
Pediatrics: The safety and effectiveness of Norpace in children have not been established.
Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose-eyes-throat, urinary retention. *Genitourinary:* urinary frequency and urgency, dysuria. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *Central Nervous System:* nervousness, depression, insomnia, impotence, dizziness, general fatigue/muscle weakness, headache, malaise. A single case of acute psychosis has been reported following Norpace therapy with prompt return to normal mental status when therapy was stopped. *Cardiovascular:* edema/weight gain, cardiac conduction disturbances, shortness of breath, syncope, chest pain, hypotension. *Dermatologic:* generalized rash/dermatoses.
Dosage and Administration: Dosage must be individualized for each patient based upon response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose. The recommended initial dosage schedule for adults is a single loading dose of 300 mg, followed by 150 mg every six hours.

For patients of small stature, or those with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation, a loading dose of 200 mg is recommended, followed by 100 mg every six hours.

For patients with severe renal insufficiency lower doses are recommended. See complete prescribing information for details.
Overdosage: No specific antidote for Norpace has been identified; treatment of overdosage should be supportive. Overdosage might be expected to produce excessive widening of the QRS complex, worsening of congestive heart failure, hypotension, varying kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects might also be observed. The electrocardiogram should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given as required. In vitro studies have demonstrated good dialyzability for disopyramide.

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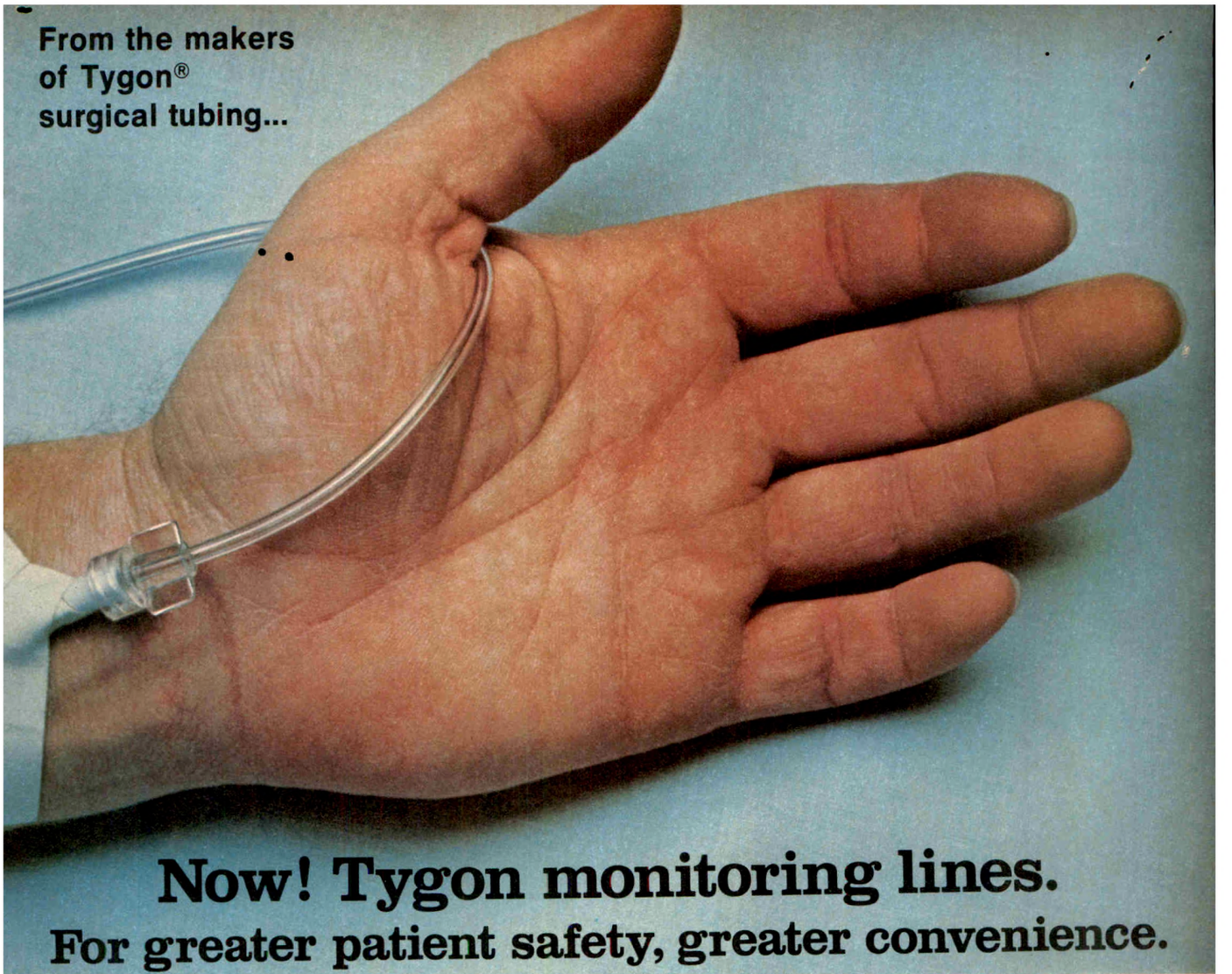

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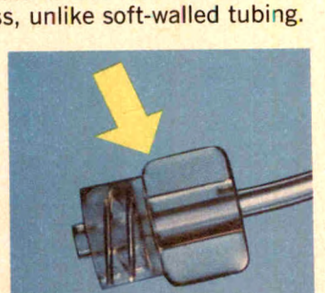

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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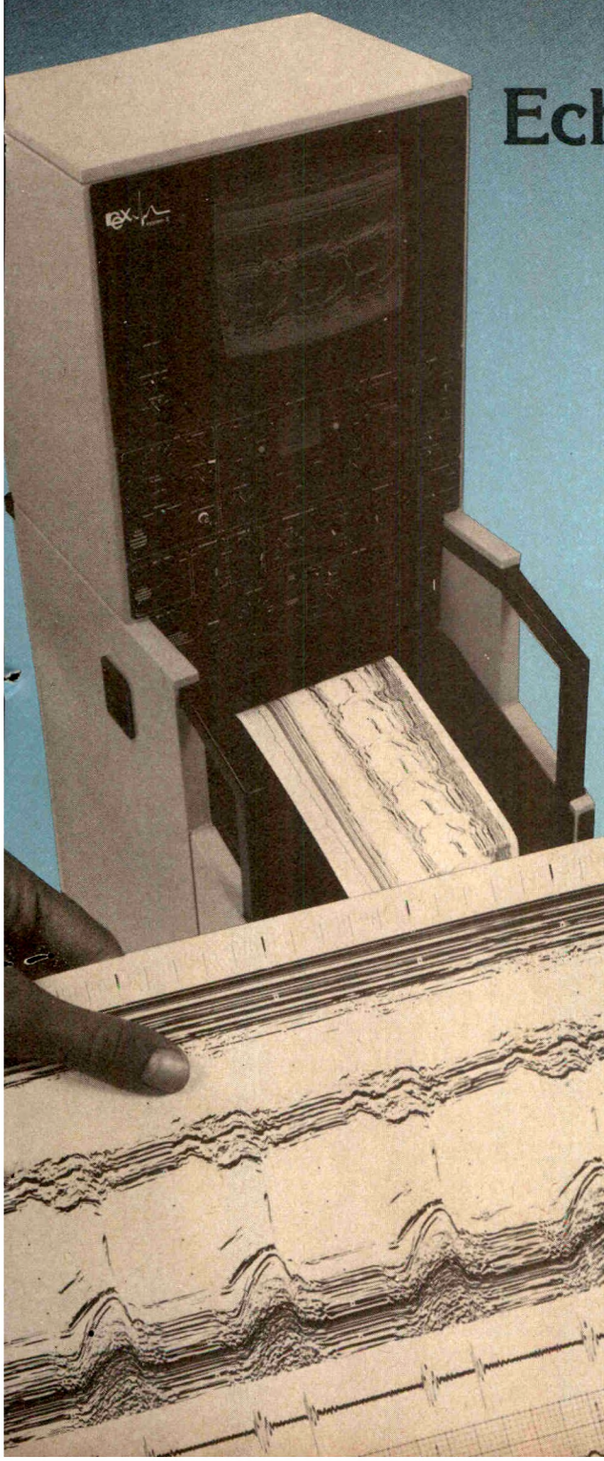

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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REFLECTION OF PROGRESS:

THE MEDTRONIC 5375 EXTERNAL PACEMAKER.

FROM THE COMPANY THAT HAS ALWAYS SET THE STANDARDS FOR EXTERNAL PACEMAKERS

From our long-standing tradition of providing products for the pacemaker patient has evolved the 5375. Engineering advancements allow the 5375 to provide safe, convenient operation for the physician, nurse and patient.

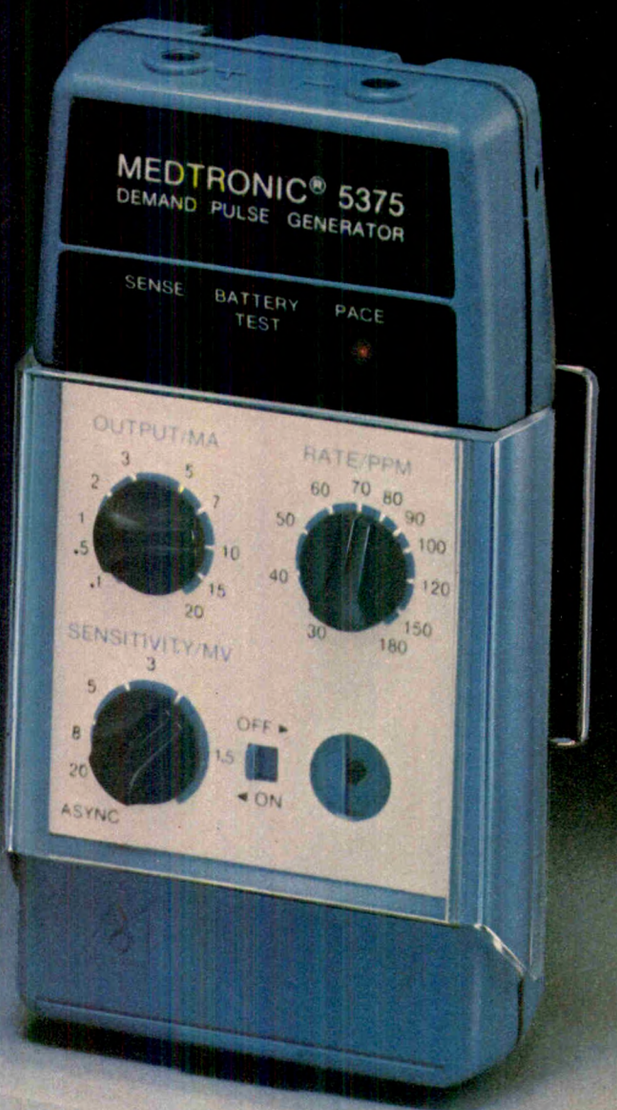
THE STANDARD OF SAFETY

5375 features provide protection against leakage current, EMI and inadvertent inhibition. Splash resistant terminal connections greatly reduce chances of contact with sources of dangerous leakage current — especially important on the busy CCU and ER service floors.

THE STANDARD OF CONVENIENCE

Cables connect by push button. Sliding transparent faceplate protects against accidental movement of controls. Retractable handles allow easy fastening of unit to patient's arm or waist. Indicator lights offer durable, visible verification of pacing, sensing and battery operation. And batteries can be changed quickly and easily, without tools, without interrupting pacing.

Evaluate the 5375. Contact Medtronic. We've been setting the standards for external pacemakers for more than 20 years.



Medtronic

Helping you help the pacemaker patient

MEDTRONIC 5375 EXTERNAL PACEMAKER PRODUCT INFORMATION

INTENDED USES
The Model 5375 External Demand Pulse Generator is intended for use in conjunction with a cardiac lead system for temporary demand or asynchronous pacing. The Model 5375 can be used where therapeutic, prophylactic or diagnostic cardiac pacing is indicated. It can also be used to estimate stimulation thresholds and the R-wave potentials sensed by the pacing lead system electrodes (see product labeling for details).

CONTRAINDICATIONS
There are no known contraindications to the use of external pacing as a means to temporarily pace the heart. The patient's age and medical condition, however, may dictate a particular external pulse generator and the lead system used by the physician.

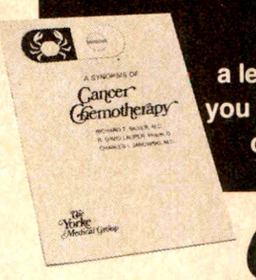
WARNINGS
A cardiac lead system constitutes a direct, low resistance current path to the myocardium. Extreme caution must be taken to properly ground all line-powered equipment used in the vicinity of the patient to protect against ventricular fibrillation induced by leakage current.

Electrosurgical units should be used with caution in the vicinity of an external pacemaker system because of the danger of introducing extrinsic currents into the heart from the external pacemaker system which could cause fibrillation. When operating in the demand mode, the pulse generator output may revert to the asynchronous mode or inhibit the pulse generator in the presence of excessive levels of interference from equipment such as: electrosurgery units, diathermy equipment and some medical telemetry systems. Defibrillation discharges will probably not affect external pulse generators.

PRECAUTIONS
The physician should be aware that the Model 5375 can malfunction for reasons such as: random component failure, battery depletion and mishandling which cannot be predicted prior to failure. The pacing lead system may malfunction at any time due to lead system-related problems. Appropriate standby equipment should be available when the Model 5375 pulse generator is used.

POTENTIAL COMPLICATIONS
Potential complications associated with the use of an external pacemaker system are asystole following abrupt cessation of pacing and lead system-related problems such as: myocardial irritability, local tissue reaction, muscle and nerve stimulation, infection, erosion of the lead system through the skin, transvenous lead-related thrombosis and embolism, myocardial lead-related hemorrhage and cardiac tamponade.

How to Keep Up with Drug Interaction in Cancer Chemotherapy



Three authorities from a leading medical center show you how to use the most current chemotherapeutic agents

A SYNOPSIS OF
Cancer Chemotherapy

At last a way to keep up with the bewildering proliferation of new chemotherapeutic drugs which have come into use relatively recently. This just published guide will be valuable to every hospital, and every oncology specialist, general internist, clinical pharmacist, and nurse oncologist.

A SYNOPSIS OF CANCER CHEMOTHERAPY is a concise, readily understandable "how to" manual. Developed originally for staff use at The New York Hospital-Cornell Medical Center, the concept proved so successful it was decided to make it available to other professionals. The new users of the SYNOPSIS have the advantage of a proven, time-tested learning system. It is written in a unique, compact work-book style to keep reading time to a minimum.

The reader can quickly find the following for both commercially available and investigational drugs:
- Structure
- Mechanism of Action
- Pharmacokinetics
- Toxicity
- Therapy
- Availability

The chemotherapeutic agents in the main listing section cover these categories:
- Alkylating Agents
- Antimetabolites
- Mitotic Inhibitors
- Antibiotics
- Miscellaneous (includes such drugs as Mithramycin, Mitotane, etc.)

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New wide-angle probe for EkoSector I.™

It gives you .. the big picture.

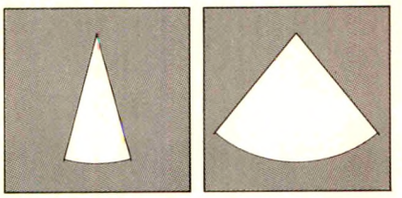
Our remarkable new wide-angle probe gives you an enlarged cross-sectional scan of the heart, making it easier for you to visualize and correlate relative position and motion patterns of intracardiac structures for a more accurate diagnosis.

In addition this new probe provides an image of extremely high resolution.

More innovation without obsolescence.

The new wide-angle probe is yet another SKI innovation designed to protect your original investment while providing extra value to you.

If you already own an EkoSector I™, a modification will enable you to use the standard probe and the new wide-angle probe interchangeably. Both heads simply attach to the existing probe handle.



The new wide-angle probe displays a scan that is 50° greater than the standard 30° probe. Both probes will be supplied with all new EkoSector I units. The wide-angle probe is supplied for existing systems as an optional accessory.

Real-time cross-sectional scanning and unique design.

The SKI patented direct processing method provides distortion-free electronic images and correct, spatially-oriented, information concerning the depth relative to the chest wall, and real-time motion of cardiac structures.

Clinically reported uses for EkoSector I include quantitation of mitral and aortic stenosis, detection of ventricular aneurysms and localization of ventricular outflow obstructions.

Transducers provide A-mode, M-mode or sector scanning of the heart or other organs. Images can be displayed on the oscilloscope or on the large external X-Y monitor. A videotape recorder allows recording of M-mode or cross-sectional scans along with verbal comments. Playback can be at normal speed, slow motion or stop-frame projection. Recorded images can be selectively altered in size by means of the tissue depth control.

If you already own an Ekoline 20A, the EkoSector I can easily be interfaced with it, cutting your cost for the whole system by almost half. Even if you do not already own an Ekoline 20A, the complete system still costs less than competing systems.

SmithKline Instruments, Inc.

880 West Maude Avenue, Sunnyvale CA. 94086 (408) 732-6000

Please send me more information on the new EkoSector I ☐ Ekoline 20A ☐

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Hospital _____

Address _____

City _____

State _____ *Zip* _____

Mail to Smith Kline Instruments, Inc. P.O. Box 1947, Sunnyvale, California 94086

Or, call 800-538-1556 toll free. In California call collect 408-732-6000.

AJC

In Canada, mail to Smith Kline Instruments, 300 Laurentien Blvd., St. Laurent, Quebec, Canada. In the United Kingdom, mail to Smith Kline Instrument Co. Ltd., Welwyn Garden City, Hertfordshire, England.

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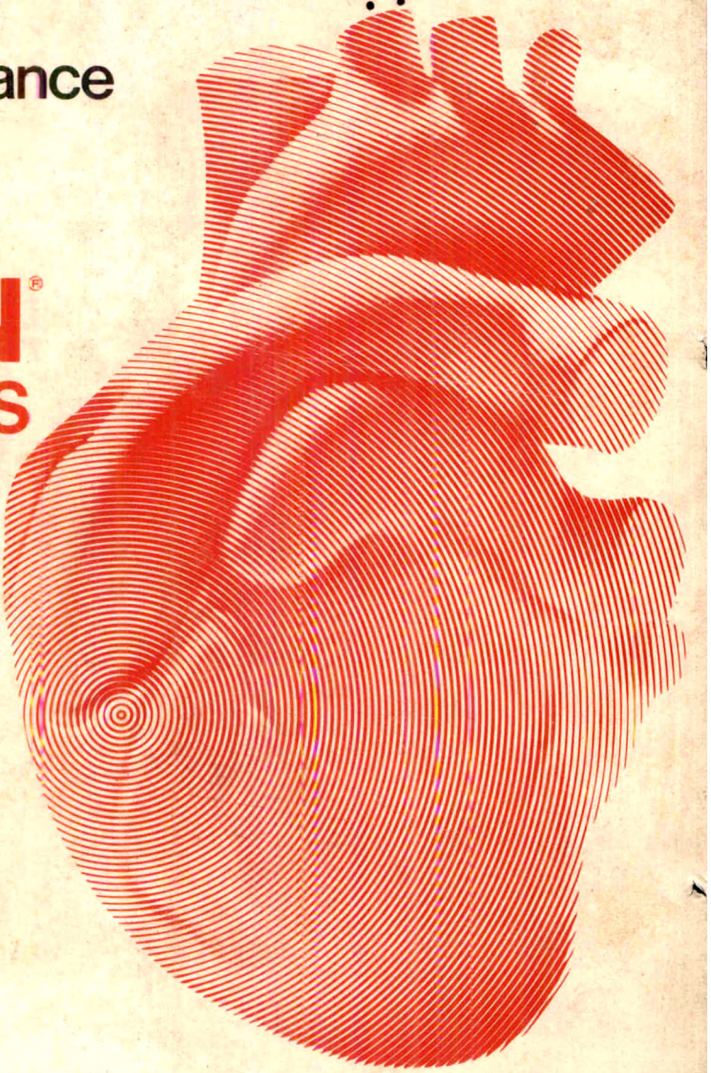
a SmithKline company

The Pacekeeper™

For the broad spectrum of cardiac arrhythmias broad-range treatment... conversion and maintenance



CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance
- ☐ Full quinidine cardiodynamics
- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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FEBRUARY 1978

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ABSTRACTS

27th Annual Scientific Session

American College of Cardiology

March 6–9, 1978, Anaheim, California

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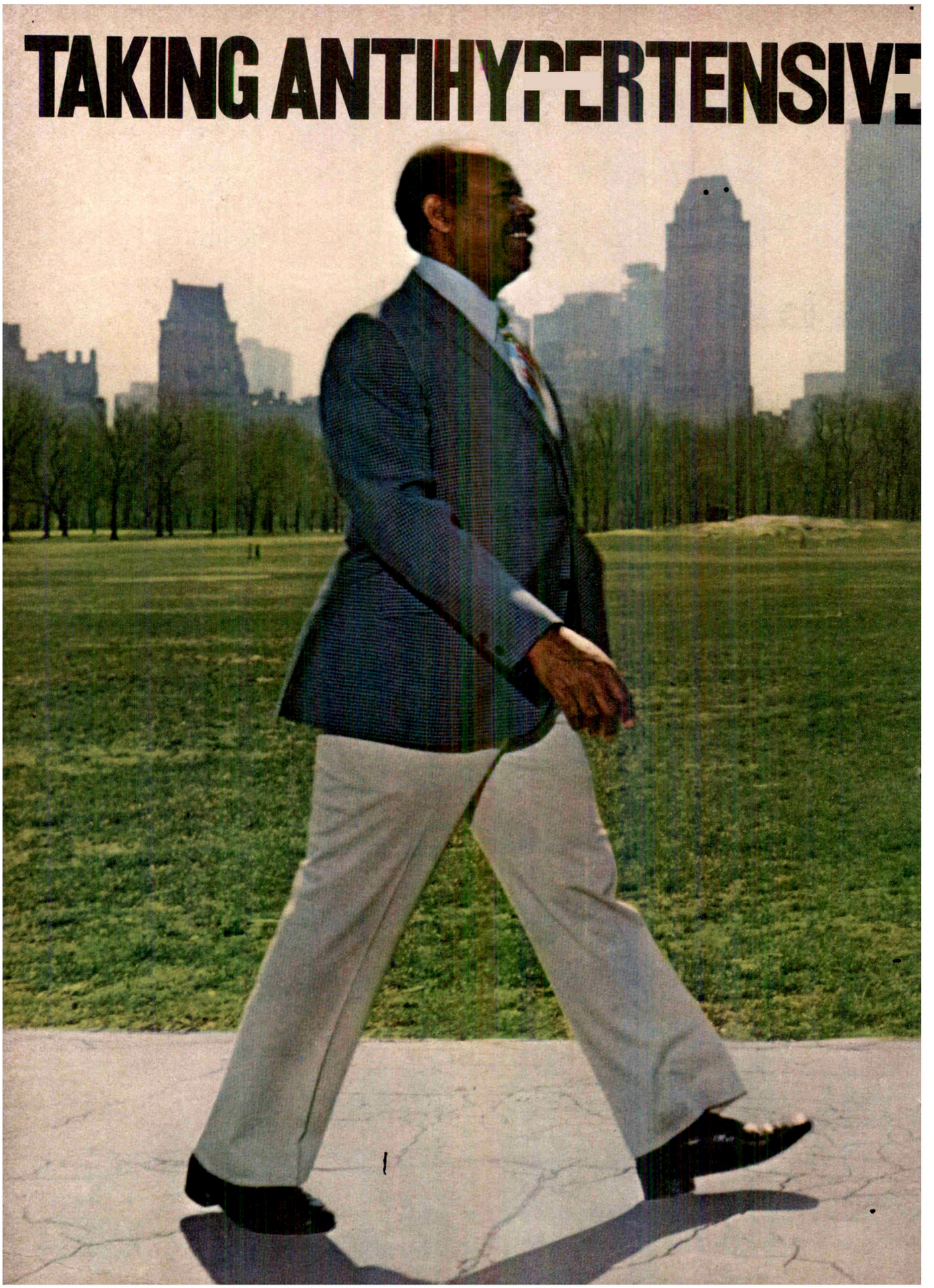
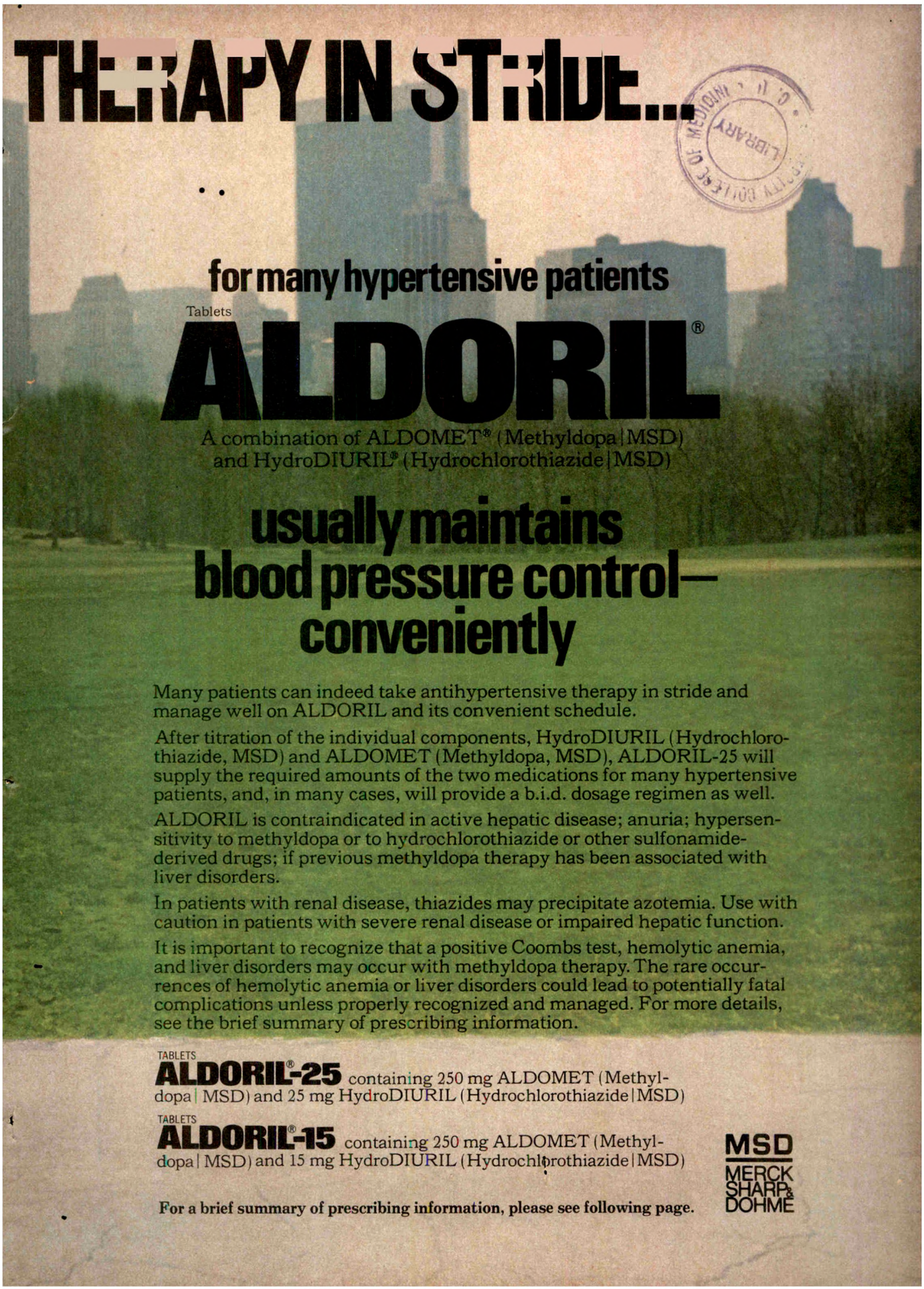
TAKING ANTIHYPERTENSIVE




THERAPY IN STRIDE...
for many hypertensive patients
Tablets
ALDORIL®
A combination of ALDOMET® (Methyldopa | MSD)
and HydroDIURIL® (Hydrochlorothiazide | MSD)
usually maintains
blood pressure control—
conveniently
Many patients can indeed take antihypertensive therapy in stride and manage well on ALDORIL and its convenient schedule.
After titration of the individual components, HydroDIURIL (Hydrochlorothiazide, MSD) and ALDOMET (Methyldopa, MSD), ALDORIL-25 will supply the required amounts of the two medications for many hypertensive patients, and, in many cases, will provide a b.i.d. dosage regimen as well.
ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders.
In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.
It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.
TABLETS
ALDORIL®-25 containing 250 mg ALDOMET (Methyldopa | MSD) and 25 mg HydroDIURIL (Hydrochlorothiazide | MSD)
TABLETS
ALDORIL®-15 containing 250 mg ALDOMET (Methyldopa | MSD) and 15 mg HydroDIURIL (Hydrochlorothiazide | MSD)
For a brief summary of prescribing information, please see following page.
MSD
MERCK SHARP & DOHME

Antihypertensive TABLETS

ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS

ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA— *Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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Now, with Accuscan, physicians can command three major diagnostic functions in the one instrument: Holter scanning; stress testing; and 12-lead resting ECG.

This complete system is engineered for fast, easy operation in your office, clinic or hospital.

The Accutape 24 cassette recorder is an integral part of the Accuscan system. This hand-size unit can record diagnostic ECG continuously for 24 hours — without patient intervention. It also permits patients to clock and mark events automatically.

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Other noteworthy features include: automatic "reverse jog"; digital rate meter; non-fade scope with freeze capability; optional arrhythmia counter — and surprising simplicity of operation.

There's much more to say about the new Accuscan, so if you're interested in leasing or purchasing or would simply like more information, phone or mail coupon below.

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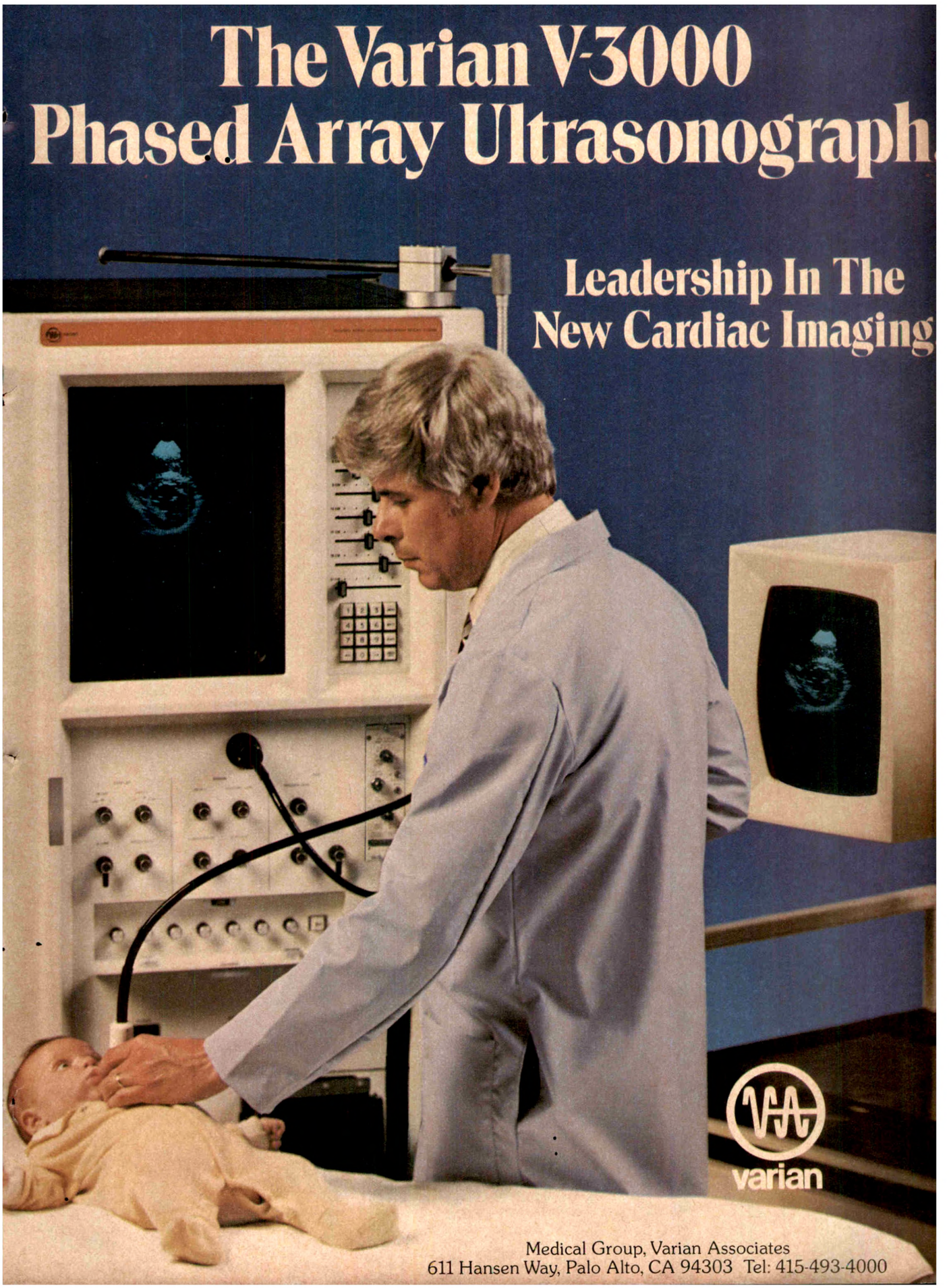
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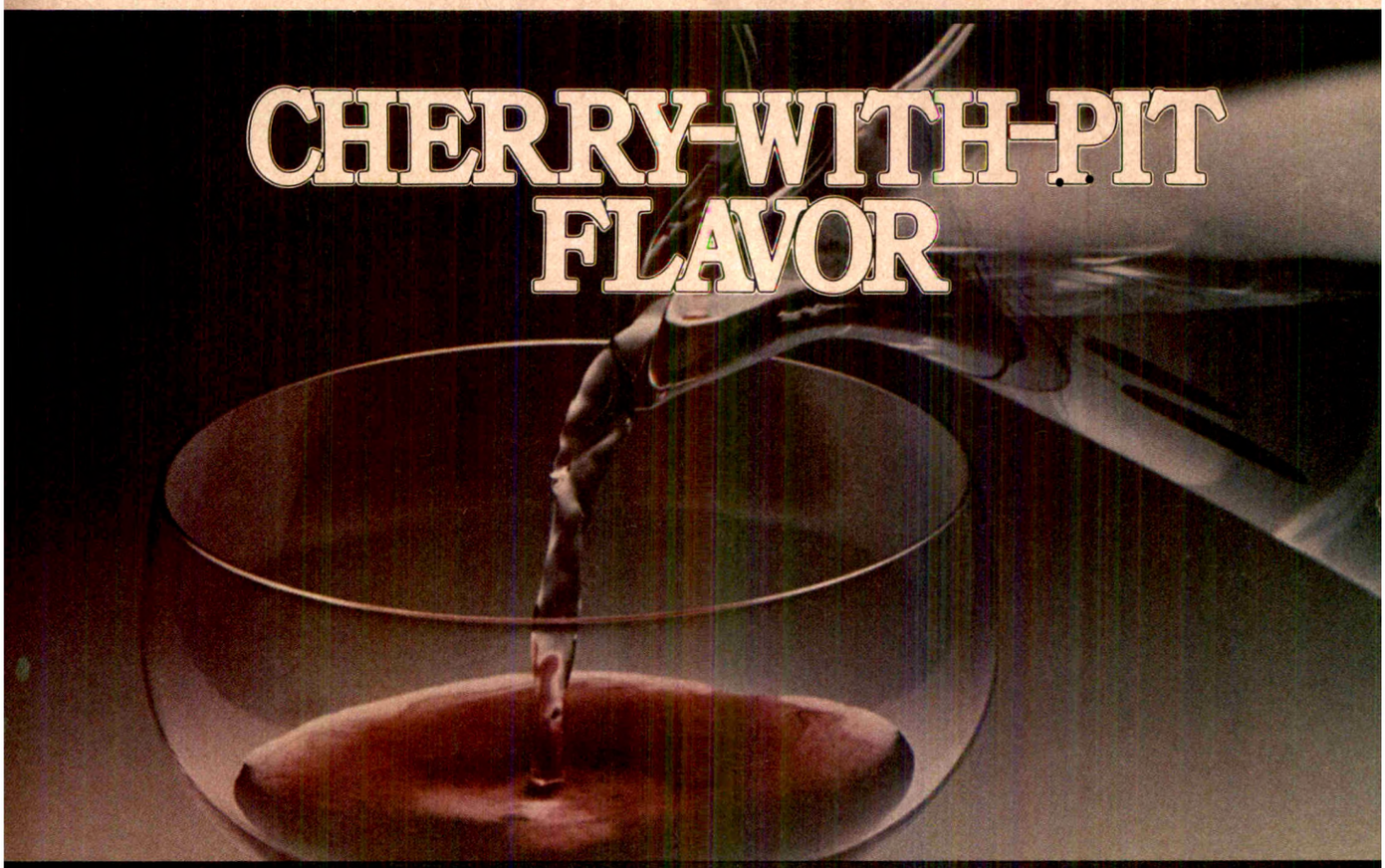

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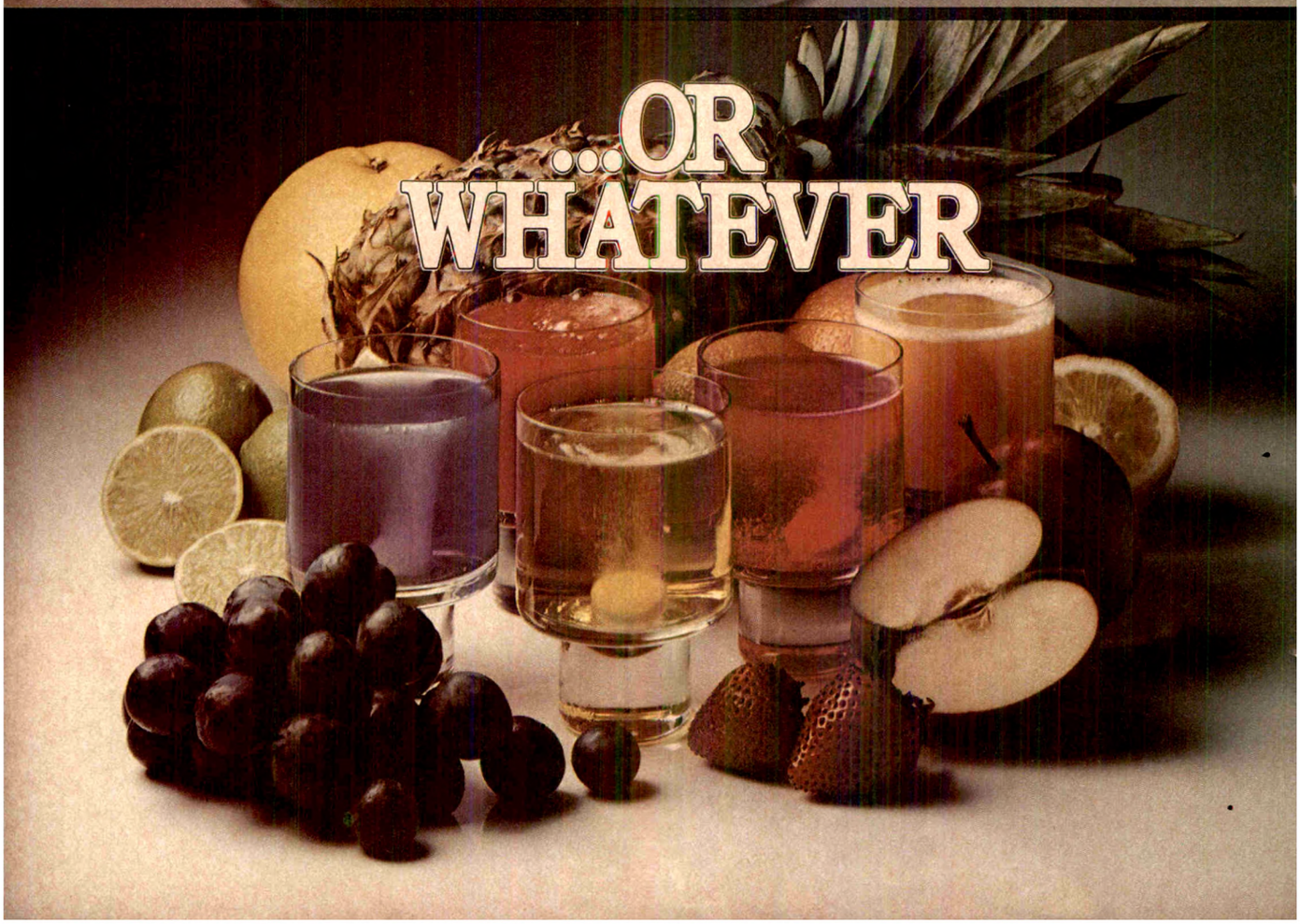

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Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

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The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

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Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

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197 **Identification of High Risk Subsets of Acute Myocardial Infarction. Derived from the Myocardial Infarction Research Units Cooperative Study Data Bank**

KARL T. WEBER, JOSEPH S. JANICKI, RICHARD O. RUSSELL and CHARLES E. RACKLEY

High risk subsets in 400 patients with acute myocardial infarction were as follows: In class I, nonsurvivors had significantly higher values for pulmonary capillary wedge pressure (16 mm Hg) and heart rate (76 beats/min); nonsurvivors in class II also had a significant elevation of pulmonary capillary wedge pressure (23 mm Hg); and in class IV the high risk subset was characterized by pulmonary capillary wedge pressure (21 mm Hg), heart rate (100 beats/min), cardiac index (1.6 liters/min per m^2), stroke index (14 cc/m^2) and stroke work index (12 g-m/m^2). Nonsurvivors in class III could not be identified from hemodynamic criteria, but the small population sample prohibits meaningful analyses and comparisons. In individual patients the clinical examination did not consistently reflect the degree of ventricular dysfunction, but careful bedside examination and hemodynamic monitoring of wedge pressure, cardiac output and heart rate together best identify the high risk patient after acute myocardial infarction. It is in these patients that an aggressive, goal-oriented management program directed at reducing myocardial energy utilization must be instituted to control infarct size and reduce patient morbidity and mortality.

204 **Coronary Anatomy and Arteriography in Patients With Unstable Angina Pectoris**

HAROLD W. ALISON, RICHARD O. RUSSELL, Jr., JOHN A. MANTLE, NICHOLAS T. KOUCHOUKOS and CHARLES E. RACKLEY

In this prospective series of 188 subjects undergoing coronary arteriography, patients with the syndrome of unstable angina pectoris usually presented with severe coronary artery disease and were candidates for coronary revascularization. Ten percent of patients with left main coronary artery disease were thought to have died as a result of cardiac catheterization because they had symptoms or evidence of myocardial necrosis within 24 hours of the procedure. The anatomic severity of coronary artery disease, primarily associated with left main coronary artery disease, appeared to be the most important factor contributing to myocardial infarction or death after cardiac catheterization. Of the patients presenting with the syndrome of unstable angina pectoris, 10.6 percent had normal coronary arteriograms. The majority of patients had severe coronary artery disease and were candidates for coronary revascularization.

210 **Tortuosity as an Index of the Age and Diameter Increase of Coronary Collateral Vessels in Patients After Acute Myocardial Infarction**

GROVER M. HUTCHINS, MARTIN M. MINER and BERNADINE H. BULKLEY

Measurements of diameter and tortuosity of 140 collateral vessels identified in postmortem coronary arteriograms of 35 autopsy patients with a myocardial infarct of known age showed that collateral diameter and tortuosity increased with time after the infarction. These results suggest that the identification of tortuosity in a coronary

Continued on page A14

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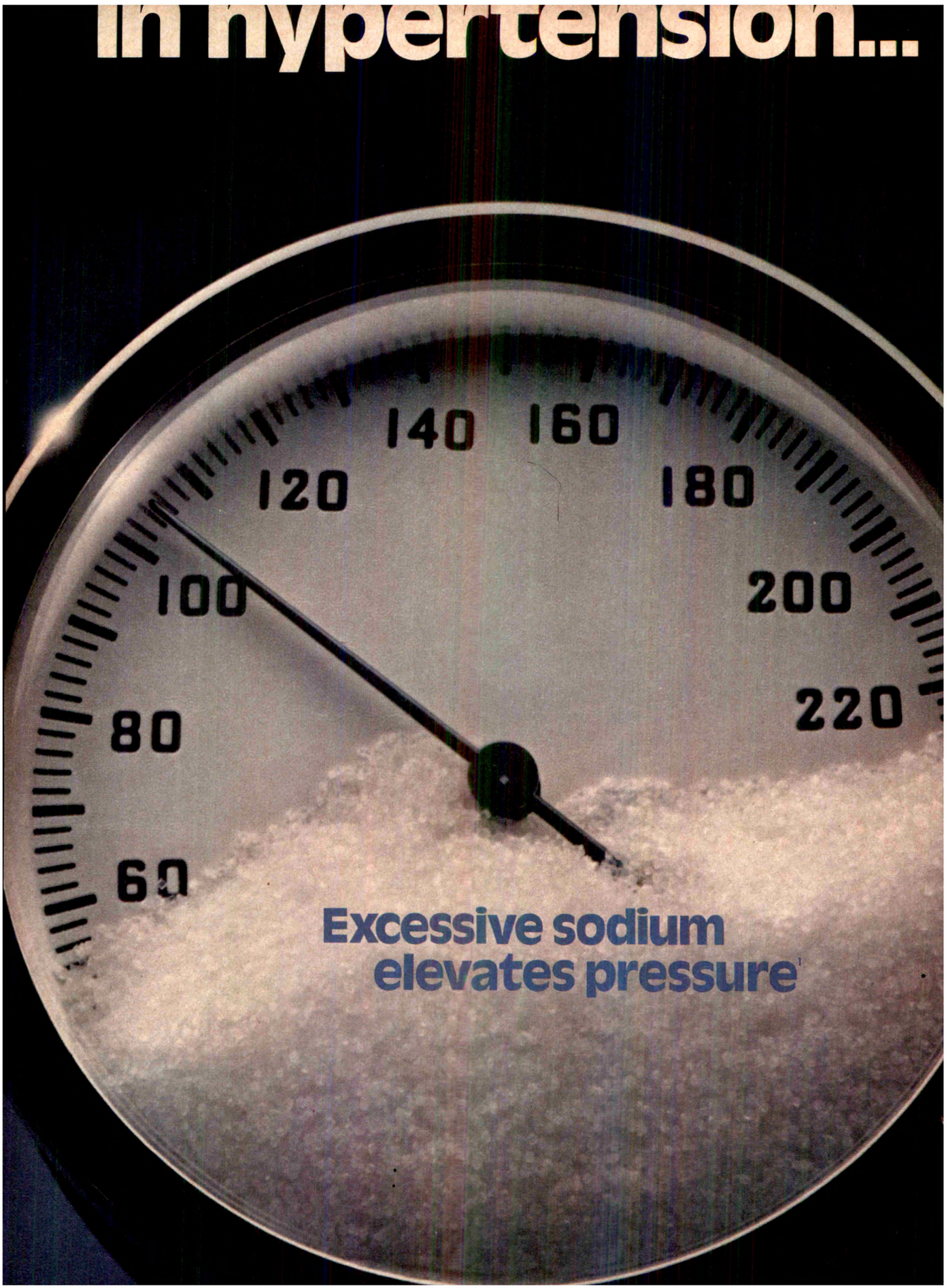

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Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

References:

1. Laragh, J.H. et al.: Vasoconstriction - volume analysis for understanding and treating hypertension: The use of renin and aldosterone profiles, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, pp. 824-825. **2.** Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: A Cooperative Study, JAMA 237:255, January 17, 1977.

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vessel may indicate its functions as a collateral channel and the degree of dilatation may be a measure of the time it has been such a collateral channel. Collateral vessels, like normal vessels, grow by both dilatation and lengthening. However, in the collateral vessel, which is constrained by relatively fixed points of origin and termination, the excess length is accommodated by increasing tortuosity.

216 Angiographic Evaluation of the Natural History of Normal Coronary Arteries and Mild Coronary Atherosclerosis

BAUDOUIN MARCHANDISE, MARTIAL G. BOURASSA, BERNARD R. CHAITMAN and JACQUES LESPERANCE

These angiographic studies in 48 patients with normal coronary arteries or nonsignificant coronary atherosclerosis who underwent a second angiogram because of persistent or recurrent chest pain showed no development of coronary disease in 22 patients with normal coronary arteries after a minimal interval of 13 months and an average interval of 52 months. The combined data suggest that middle-aged adult men and women with normal coronary arteries rarely manifest subsequent coronary arteriosclerosis. In the 26 patients with minimal lesions, 27 percent showed progression of coronary disease on restudy after an average interval of 3 years. Because these studies dealt with a select group of symptomatic patients, these conclusions may not be applicable to unselected asymptomatic men and women.

221 Incidence and Significance of Decreases in Systolic Blood Pressure During Graded Treadmill Exercise Testing

STEPHEN N. MORRIS, JOHN F. PHILLIPS, JOHN W. JORDAN and PAUL L. McHENRY

In this group of 460 patients with definite or suspected coronary heart disease a sustained exercise-induced decrease in peak systolic blood pressure of 10 mm Hg or more was a highly specific sign of multiple vessel coronary artery disease, especially when cardiomyopathy or significant heart valve disease was absent. Acute left ventricular pump failure secondary to extensive myocardial ischemia best explains this phenomenon. Decreases in blood pressure were not observed during 650 maximal exercise tests performed by 560 clinically normal men or by 6 patients after coronary bypass graft surgery.

227 Significance of Chest Pain During Treadmill Exercise: Correlation With Coronary Events

JOHN P. COLE and MYRVIN H. ELLESTAD

This follow-up study of 1,402 patients with a positive maximal treadmill stress test shows that angina during exercise identified 85 percent of true positive tests for coronary artery disease, whereas S-T depression alone identified only 64 percent of such tests. Coronary events (myocardial infarction, progression of angina and coronary death) were twice as frequent in subjects with angina and S-T segment depression as in those without angina. The incidence of coronary events was more than twice as great when the angina was induced by a light work load (4 METS) as when it was induced by a heavy work load (8 to 9 METS). In women, chest pain during the abnormal treadmill test was a less useful prognosticator of future coronary events than in men.

233 Plasma Norepinephrine in Congestive Heart Failure

JAMES A. THOMAS and BERNARD H. MARKS

This study demonstrates that plasma norepinephrine concentration in patients with congestive heart failure due to atherosclerotic heart disease, congestive cardiomyopathy or hypertensive cardiovascular disease is directly related to the degree of left ventricular dysfunction. Progressively increasing plasma concentrations of norepinephrine significantly prolonged the preejection period but reduced the left ventricular ejection time. Plasma lymphocytes from patients with the greatest degree of left ventricular dysfunction failed to generate normal amounts of cyclic 3′,5′-adenosine monophosphate after beta adrenergic receptor stimulation with isoproterenol, suggesting that beta adrenergic receptors are desensitized in these patients and that this desensitization contributes to the observed alterations in myocardial contractility.

Continued on page A17

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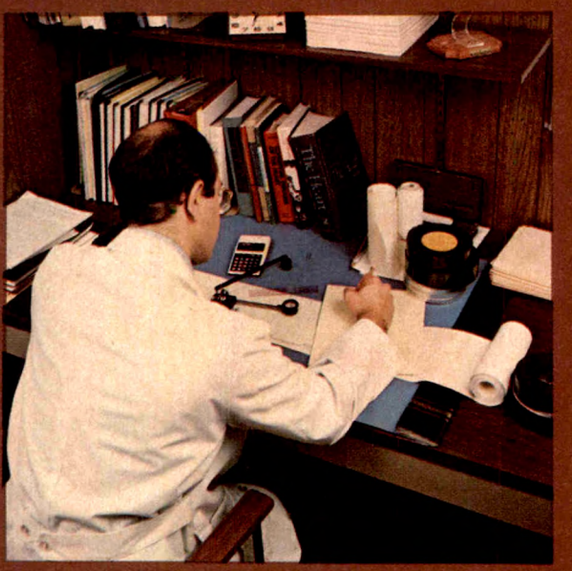

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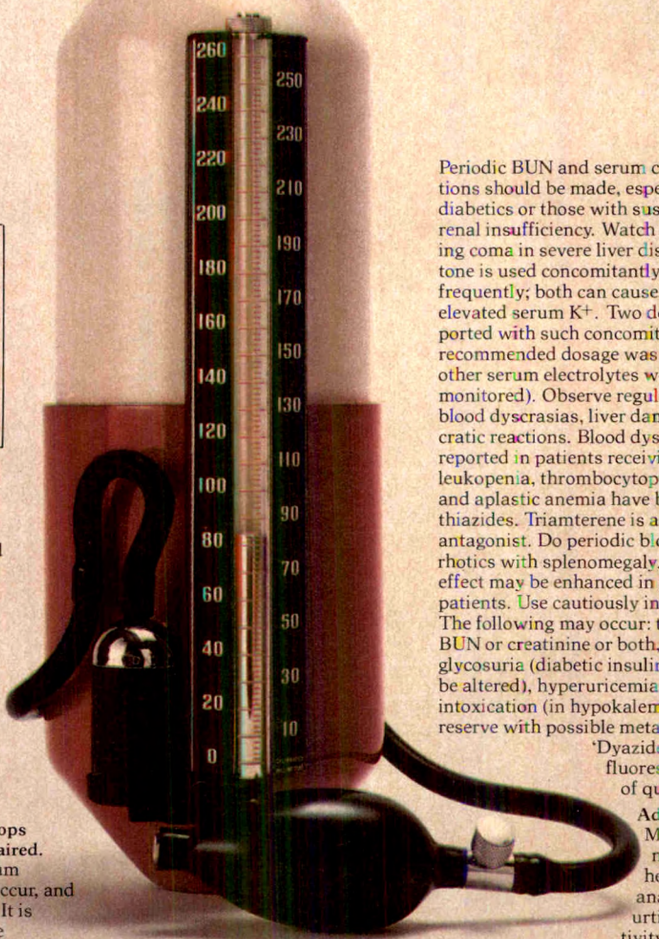

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***Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

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EXPERIMENTAL STUDIES

244 **Electrophysiologic Studies on Atrioventricular Nodal Wenckebach Cycles**

MICHAEL B. SIMSON, JOSEPH F. SPEAR and E. NEIL MOORE

With the aid of programmed stimulation, Wenckebach cycles with a 4:3 ratio were produced by rapid atrial pacing and studied in 27 anesthetized denervated dogs. All animals showed a progressive increase in atrioventricular (A-V) nodal refractoriness in the effective refractory period for each beat and a rightward shift of the A′-H′ relative to the A-A′ refractory curves. In Wenckebach cycles there is a progressive increase in refractoriness, caused by cumulative effect similar to that seen after a blocked beat during stressed 1:1 conduction, until block occurs and the cycle resets. No evidence for overt or concealed reentry was found during anterograde Wenckebach cycles. It appears most likely that Wenckebach cycles and reentry are associated conditions, not necessarily causally related.

259 **Myocardial Hemorrhage After Coronary Reperfusion in Pigs**

ROBERT J. CAPONE and ALBERT S. MOST

Occlusion of the left anterior descending coronary artery for 1 hour in anesthetized closed chest pigs using an intracoronary balloon occluding technique resulted in the occurrence of postreperfusion myocardial hemorrhage in an animal with a coronary circulation similar to man's. The hemorrhage was directly related to the duration of occlusion and was unaffected by mannitol given before reperfusion or general anesthesia. In the pig the critical period with respect to intramyocardial hemorrhage lies between occlusion times of 15 and 60 minutes. No improvement was observed in function of the most depressed left ventricular segment or adjacent segments during reperfusion. These results suggest that additional measures may be necessary to reduce temporary occlusion time or otherwise improve vascular integrity during revascularization surgery in man.

METHODS

267 **Noninvasive Assessment of Coronary Stenoses by Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilatation. I. Physiologic Basis and Experimental Validation**

K. LANCE GOULD

These results from 145 external myocardial perfusion images of thallium-201 and technetium-99M–labeled particles obtained at rest, during exercise or after coronary vasodilators in 20 dogs with mild to severe coronary stenoses demonstrated the following: (1) The ratio of maximal flow in a normal to stenotic coronary artery must be at least 2:1 before defects appear in the myocardial perfusion image of thallium-201. (2) A diagnostic technique that utilizes a maximal stimulus for increasing coronary flow and an imaging agent that is distributed to the myocardium in linear proportion to coronary flow at flow rates up to four or five times resting levels will be the most sensitive method for detecting mild coronary stenosis. Furthermore, the effect of intravenously administered dipyridamole on the coronary circulation can be closely regulated by adjusting the dose rate of infusion and can be instantaneously reversed with intravenous administration of aminophylline, a dipyridamole antagonist.

279 **Noninvasive Assessment of Coronary Stenoses by Myocardial Imaging During Pharmacologic Coronary Vasodilatation. II. Clinical Methodology and Feasibility**

K. LANCE GOULD, R. JEFFREY WESTCOTT, PETER C. ALBRO and GLEN W. HAMILTON

A noninvasive method utilizing myocardial imaging of thallium-201 injected intravenously at rest and during coronary vasodilatation induced with intravenously administered dipyridamole, a patent selective coronary vasodilator, is shown to be feasible as a routine diagnostic procedure in 62 patients. However, it is necessary to pay close attention to dose rates of infusion, timing of thallium injection, body position and proper monitoring of the patient's blood pressure, electrocardiogram and clinical symptoms. Patients with angina pectoris at rest should not be studied with dipyridamole because diagnostic image defects would be expected without introduction of a stress. These initial results warrant a larger clinical study to define the diagnostic sensitivity and specificity of the technique.

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PEDIATRIC CARDIOLOGY

288 **New Serial Contrast Technique for Assessment of Left to Right Shunting Patent Ductus Arteriosus in the Neonate**

HUGH K. ALLEN, DAVID J. SAHN and STANLEY J. GOLDBERG

A new serial echocardiographic contrast technique for detection of patent ductus arteriosus demonstrated a left to right shunt in 30 of 33 prospectively studied premature infants. This serial study also helped elucidate the natural history of patent ductus arteriosus. Twenty-four of the 30 patients with a positive study initially had a left to right shunting patent ductus arteriosus without an audible murmur. Three of these patients later had congestive heart failure, and two required operative ligation of the patent ductus. The high rate of detection of silent patent ductus arteriosus and its bedside confirmation when suspected are important in the serial management of critically ill newborns with this condition. The only potential hazards are related to the safety of umbilical arterial catheters.

295 **Abnormal Right Ventricular Size and Ventricular Septal Motion After Atrial Septal Defect Closure. Etiology and Functional Significance**

ALAN S. PEARLMAN, JEFFREY S. BORER, CHESTER E. CLARK, WALTER L. HENRY, DAVID R. REDWOOD, ANDREW G. MORROW and STEPHEN E. EPSTEIN. *With the technical assistance of Cora Burn, RN, Estelle Cohen and F. Joyce McKay, RN*

To determine the significance of postoperative echocardiograms that demonstrate persistent right ventricular dilatation and paradoxic ventricular septal motion after repair of an atrial septal defect, 31 patients were studied before and after repair of an atrial septal defect. These echocardiographic abnormalities correlated with age at operation and length of postoperative follow-up study but not with the degree of preoperative right ventricular enlargement, shunt size or right ventricular pressure before or after operation. These abnormalities do not indicate incomplete closure of the atrial septal defect. Abnormalities of ventricular septal motion may be partly related to the posterior displacement of the septum within the heart at end-diastole (as a consequence of right ventricular dilatation) but not to the nature of the hemodynamic burden causing such dilatation.

REPORTS ON THERAPY

302 **Nitroglycerin-Induced Improvement in Exercise Tolerance and Hemodynamics in Patients With Chronic Rheumatic Heart Valve Disease**

JEFFREY S. BORER, DAVID R. REDWOOD, SAMUEL B. ITSCOITZ, ROBERT E. GOLDSTEIN and STEPHEN E. EPSTEIN

The short-term administration of nitroglycerin increased exercise capacity and the hemodynamic response to mild and intense upright exercise in 11 severely symptomatic patients with various ranges of rheumatic heart valve disease who had already received optimal conventional therapy. Nitroglycerin decreased systemic and pulmonary arterial pressures, increased heart rate and cardiac output, produced a small but significant increase in maximal oxygen consumption and improved exercise capacity. The mechanisms responsible for this nitroglycerin-mediated improvement in hemodynamics and cardiac function during exercise are probably related primarily to the peripheral venous and arteriolar dilatation produced by the drug. Additional studies appear indicated to determine the efficacy of long-term administration of nitrates in patients with rheumatic heart disease.

308 **Atrial Pacing for Cardioversion of Atrial Flutter in Digitalized Patients**

GOPAL DAS, KAMANAHALLY M. ANAND, KAUR ANKINEEDU, TRIAM CHINNAVASO, FREDERICK N. TALMERS and ARNOLD M. WEISSLER

Atrial pacing successfully converted atrial flutter on 43 occasions (98 percent) in 31 of 32 consecutive digitalized patients with this arrhythmia. One patient required transthoracic direct current synchronized countershock car-

Continued on page A20

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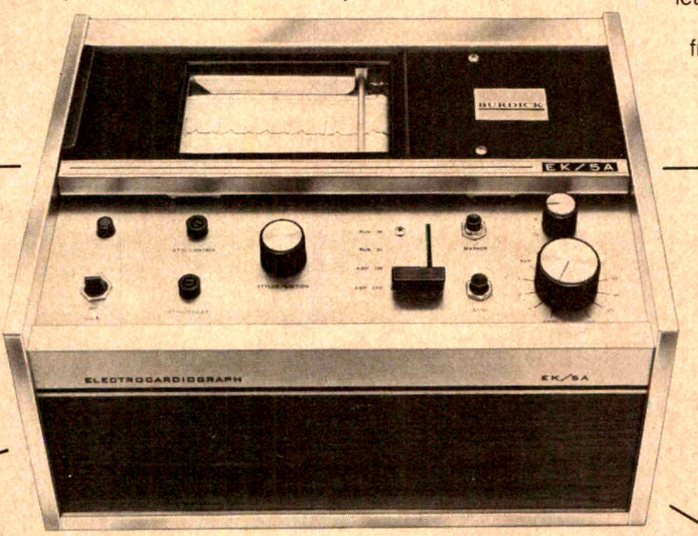

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dioversion. With atrial pacing the atrial flutter reverted immediately to sinus mechanism in 20 instances. There were 23 episodes of atrial fibrillation; 11 of the latter reverted to sinus rhythm within 24 hours. Immediately after the rhythm conversion three patients had periods of severe sinus bradycardia (heart rate 30 to 40 beats/min) and required cardiac pacing. One patient with persistent sinus bradycardia and a prolonged sinus recovery time required a permanent transvenous pacemaker.

313 **Multiple Bolus Technique for Lidocaine Administration During the First Hours of an Acute Myocardial Infarction**

MILFORD G. WYMAN, DAVID LALKA, LUCILLE HAMMERSMITH, DAVID S. CANNOM and BRUCE N. GOLDREYER

Multiple bolus injections of lidocaine every 5 minutes, if ventricular extrasystoles are not controlled, to a total of 225 mg over 16 minutes provide adequate blood levels, result in no significant toxicity and may be safely used with excellent results in patients with infarction, even in the presence of moderate congestive heart failure. The mean plasma level at the end of the last infusion was only 2.3 μg/ml. In this study the half-life of lidocaine after the first bolus dose was approximately 8 minutes in patients with class 0–1 failure, but only 4 minutes in those with class II–III failure. The clinical effect of a single bolus dose may last no longer than a few minutes. For patients with shock or pulmonary edema one half of the dose is recommended.

318 **Effects of Digitalis on Sinus Nodal Function in Patients With Sick Sinus Syndrome**

ZAKAUDDIN VERA, RICHARD R. MILLER, DON McMILLIN and DEAN T. MASON

This study dispels the fears of clinicians that digitalis may be harmful in patients with sick sinus syndrome. Assessment of the effects of digitalization in 14 patients with sick sinus syndrome, using ambulatory Holter monitoring of the electrocardiogram, treadmill exercise testing and sinus nodal recovery time determinations, clearly showed that digoxin does not exert adverse effects on sinus nodal function and can be safely used in such patients when indicated for cardiac pump dysfunction or for control of tachyarrhythmia. Digitalis produces the favorable effects of decreasing sinus nodal recovery time and eliciting ectopic escape pacemakers. The sinus nodal response to exercise was unaffected after digitalization.

324 **Effects of Morphine Sulfate on Human Coronary Blood Flow**

DAVID M. LEAMAN, STEPHEN H. NELLIS, ROBERT ZELIS and JOHN M. FIELD

The intravenous injection of morphine in 10 patients produced slight coronary vasodilation, in marked contrast to the significant coronary vasoconstriction reported in the unanesthetized dog. Four patients with normal coronary arteries showed a mild increase in coronary blood flow after morphine, whereas six with coronary artery disease showed no change. In general coronary blood flow increased from a baseline value of 104.4 ± 13.4 to 113.0 ± 17.4 ml/min (difference not significant) 15 minutes after the administration of morphine. Because morphine did not significantly alter myocardial oxygen requirements or coronary blood flow, it remains a safe drug to use in patients with heart disease, as countless years of clinical experience have proved.

REVIEW

327 **The Myocardial Supply:Demand Ratio—A Critical Review**

JULIEN I. E. HOFFMAN and GERALD D. BUCKBERG

Animal experiments indicate that relative subendocardial ischemia (a reduced inner-outer flow ratio) can be accurately predicted from the ratio of two pressure-time areas: DPTI, the area between diastolic aortic and left ventricular pressures, and SPTI, the area beneath the systolic left ventricular pressure curve. However, caution is needed in applying these results to man. The critical DPTI:SPTI ratio below which subendocardial ischemia

Continued on page A22

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occurs is about 0.4 to 0.5. This critical ratio is not independent of absolute coronary diastolic pressure and is much lower than 0.4 when coronary pressures are high. As more precise physiologic studies of the ratio are made in patients with coronary arterial obstruction, it should be possible to be more accurate in deciding what is occurring to subendocardial blood flow and oxygen supply.

DIAGNOSTIC SHELF

333 **Group Teaching of Auscultation. Use of a New Wireless Stethoscope-Type Headphone**

ANTONIO C. deLEON, Jr., W. PROCTOR HARVEY, DAVID CANFIELD and EDWARD JOHNSON

The use of an infrared beam as a mode of transmission for sound and physiologic events opens up the potential for transmission also of the electrocardiographic signal and of palpatory events. This technique using a new wireless stethoscope-type headphone enables the simultaneous transmission of heart sounds and murmurs to large groups of persons without the need for hard-wire connections to the amplifying device. The method facilitates teaching of cardiac auscultation at the bedside and in the conference room.

CASE REPORTS

336 **Successful Treatment of Drug-Resistant Atrial Tachycardia and Intractable Congestive Heart Failure With Permanent Coupled Atrial Pacing**

EMANUEL R. ARBEL, HOWARD C. COHEN, RICHARD LANGENDORF and GERALD GLICK

A specially designed implantable pacemaker for coupled atrial stimulation was successfully used to treat an adolescent patient with severe congestive heart failure associated with repetitive drug-resistant supraventricular tachycardia. During a 4 year follow-up period this treatment eliminated the tachycardia; the heart size returned to normal and the patient went on to complete clinical recovery. The necessary electrophysiologic conditions for ventricular slowing by coupled atrial pacing include an atrial effective refractory period shorter than that of the atrioventricular junction and depolarization of the ectopic atrial pacemaker by the responses to coupled atrial stimulation. This technique appears to be effective as a method of treatment in selected cases of drug-resistant chronic ectopic atrial tachycardia.

341 **Use of a Double Atrial-Triggered Standby Pacemaker System for a Patient With a Biventricular Bypass Heterotopic Cardiac Homograft**

BRIAN M. KENNELLY, LAURENCE W. PILLER, PETER P. TARJAN, JACQUES G. LOSMAN, CHRISTIAAN N. BARNARD and WALTER BECK

A double atrial-triggered standby pacemaker system was implanted to allow sequential atrial pacing of both hearts in a patient with a biventricular bypass heterotopic cardiac homograft. The design permitted either the recipient or the donor heart to dictate the rate of its fellow, depending on which heart had the faster spontaneous sinus rate. The potential benefit of sequential contraction of the donor and recipient hearts is that systole of the recipient left ventricle was isovolumic when it occurred synchronously with systole of the healthier donor left ventricle. Alternative systems for achieving sequential contractions of the two hearts were also considered, but these would not permit either heart to dictate the rate of the other.

EDITORIALS

345 **Perplexities and Complexities Concerning the Myocardial Infarction Border Zone and Its Salvage**

RICHARD H. HELFANT, VIDYA S. BANKA and MONTY M. BODENHEIMER

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Specificity and Sensitivity of Technetium-99m Pyrophosphate Myocardial Imaging in Acute Myocardial Infarction—M. Ahmad, D. S. Berman and D. T. Mason

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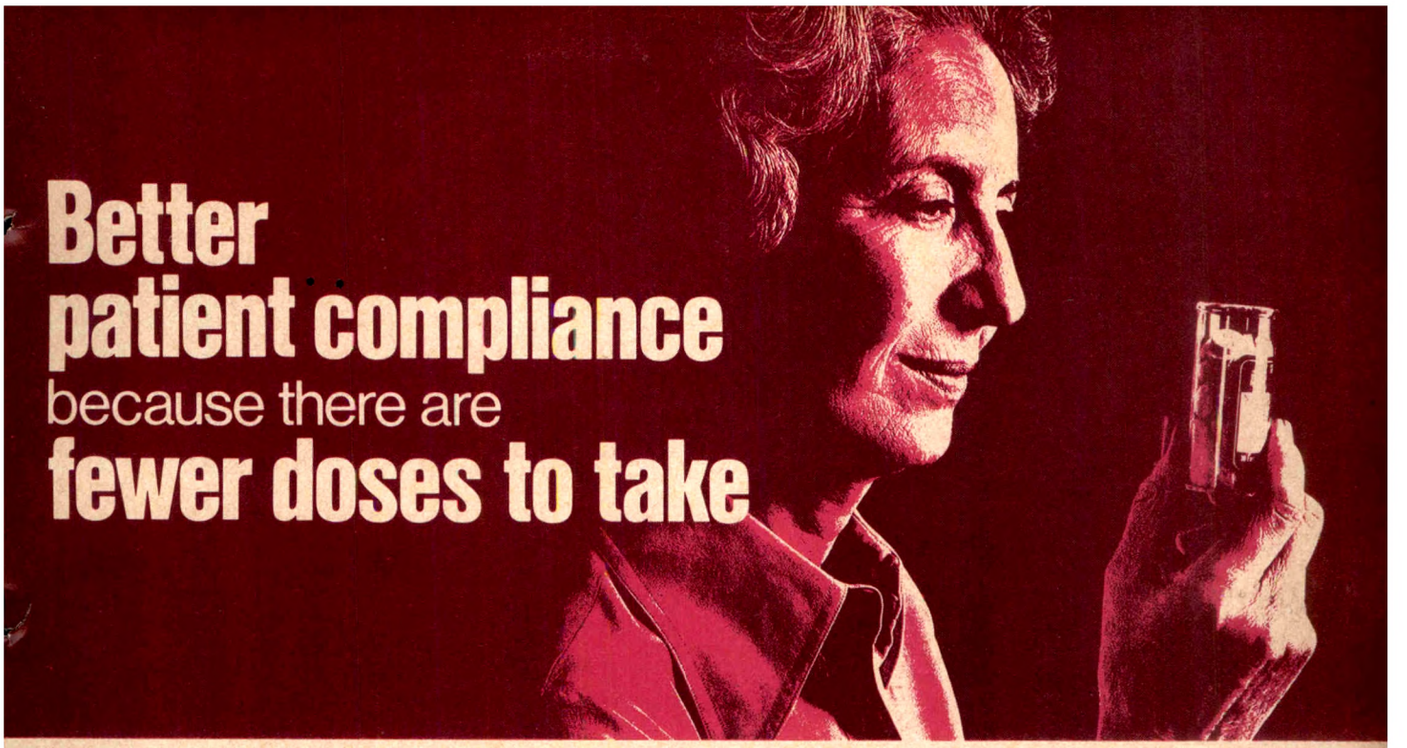

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NOTE: Depending upon the response desired, the dosage may need to be varied and the blood level and/or electrocardiographic response closely monitored during initial treatment.

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

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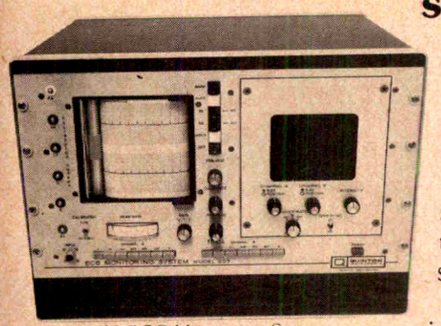


Model 623 ECG Monitoring System

The Quinton Model 623 gives you pushbutton lead selection and lets you display and record any two leads simultaneously. With the QRS Sync feature, each consecutive QRS complex can be expanded to the full width of the screen, making even small changes obvious immediately.

No battery packs are required with the 623 and the internal calibration system not only checks the recorder before you conduct a test, it also checks the oscilloscope, patient cables and heart rate meter to assure you of total system accuracy.

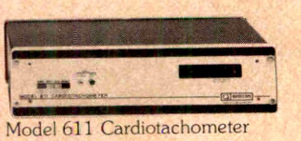
Build the system as your practice grows. Quinton offers a number of special purpose units which will expand the system's capabilities as your needs grow.

A Quinton programmer allows you to concentrate on the monitor and the patient while the test progresses automatically.

Treadmill Programmer

The Quinton ECG Data Computer digitally displays the heartrate, S-T level and S-T slope. It averages the signal to help you "see through" noisy ECG, and it records heartrate, S-T changes, arrhythmias and 20 beat ECG averages.

Model 740 ECG Data Computer



Model 611 Cardiotachometer

The Quinton cardiotachometer computes and digitally displays heartrate on an instantaneous, beat-by-beat basis. For details on all these products, contact Quinton Instrument Co., Dept. E16, 2121 Terry Avenue, Seattle, Washington 98121. Call 206/223-7373 or dial toll free 800-426-0538. **QUINTON**

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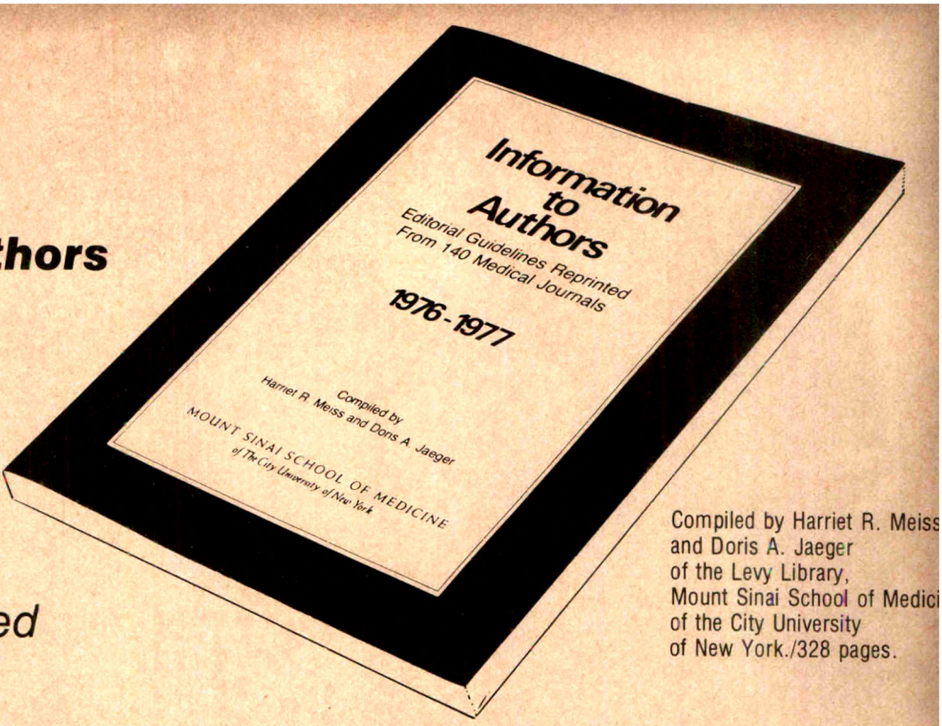

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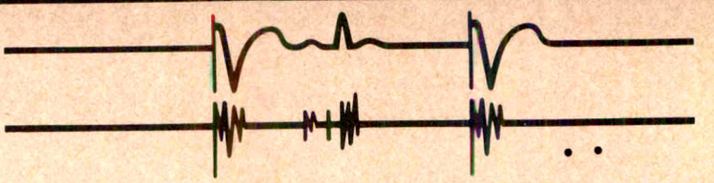

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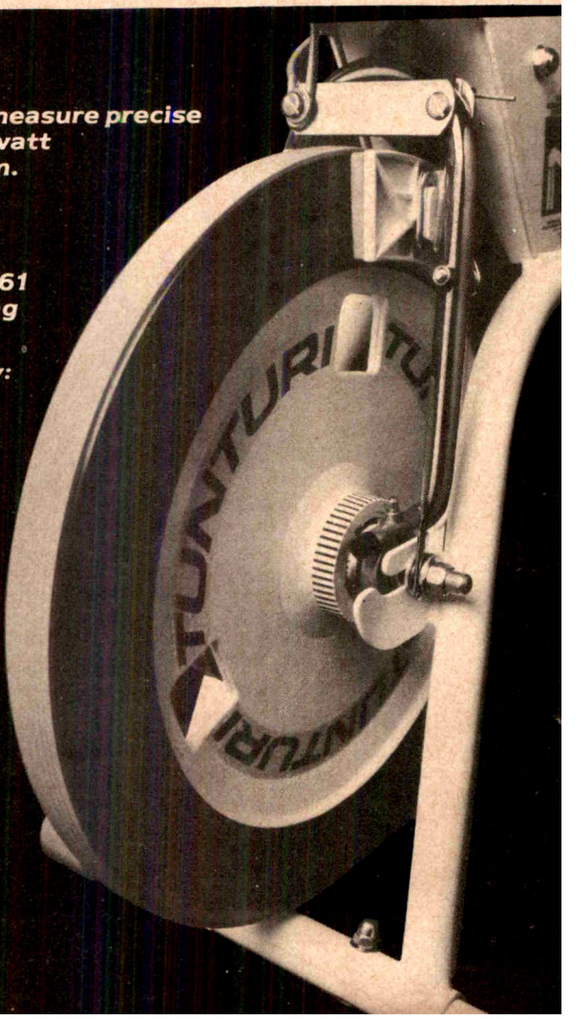

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CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.
WARNING: Do not use excessively.
PRECAUTIONS: Administer with caution and adjust to the requirements of the individual patient. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
Patients should be cautioned to adhere to dilution instructions.
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OVERDOSAGE: In case of excessive use resulting in hyperkalemia or potassium intoxication, discontinue potassium chloride administration or take other steps to lower serum levels if indicated.

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Help assure that your older patients take medications properly by printing your instructions in large letters. You might also send a copy of the instructions to the patient's spouse. Please forward your compliance tip to Cooper Laboratories, 300 Fairfield Road, Wayne, N.J. 07470, Att: W.F. Cronin.

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PRONESTYL® TABLETS (Procainamide Hydrochloride Tablets)
PRONESTYL® CAPSULES (Procainamide Hydrochloride Capsules U.S.P.)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as capsules and veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.
CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.
ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.
PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.
ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.
HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) and Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg. and 500 mg. tablets and capsules are also available in bottles of 1000.

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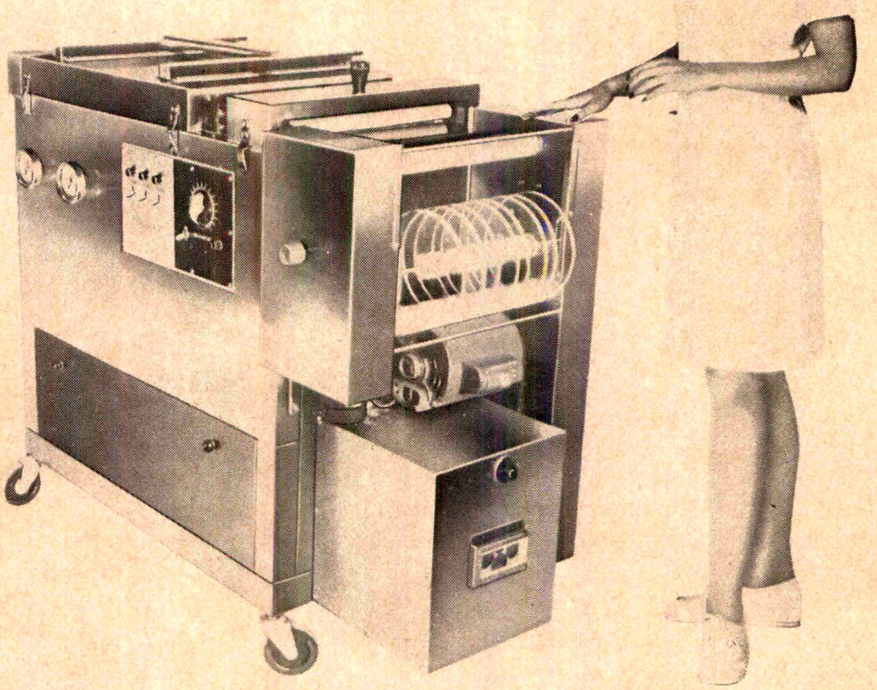

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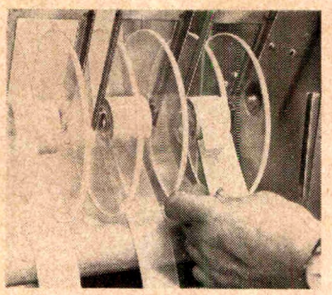

Operator removes finished reel from machine while other tracks continue to be processed.

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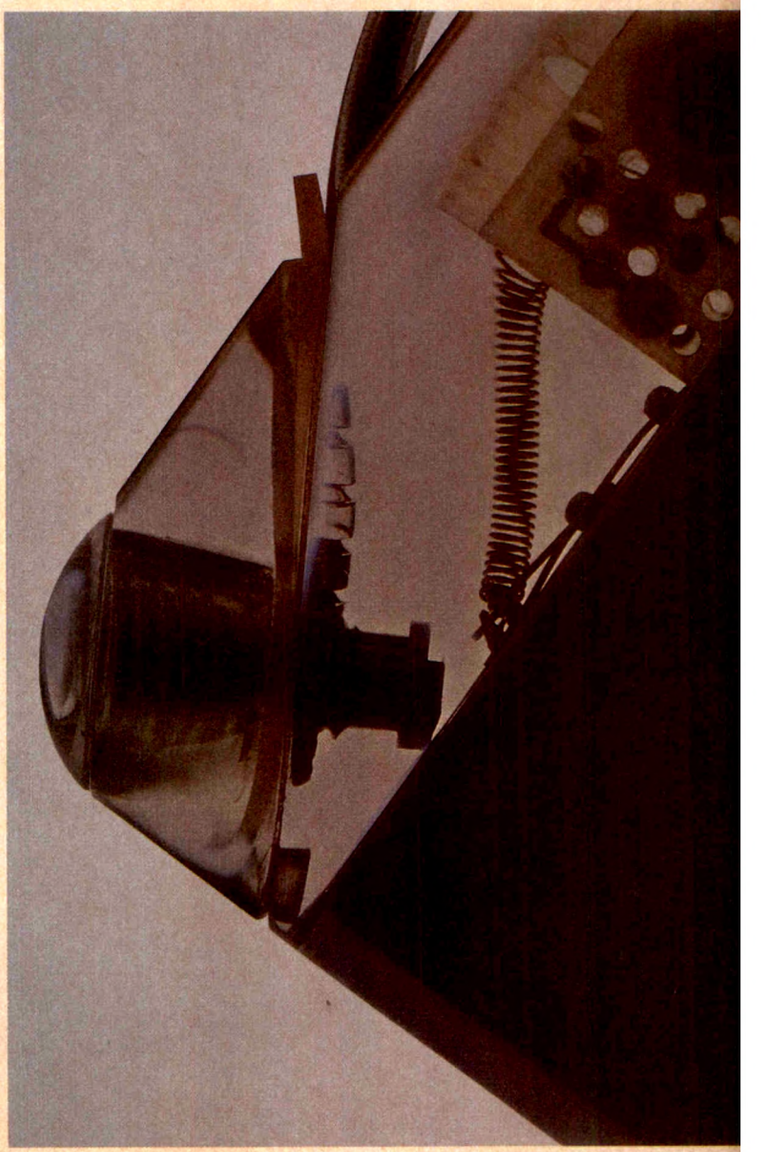
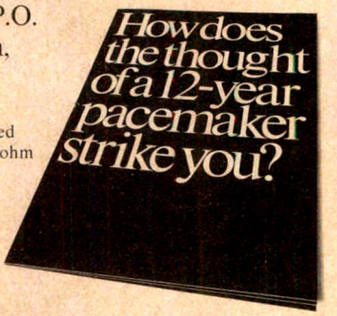
To arrange for a Vitatron representative to call on you, call (617) 964-1980. Or write for our 16-page, full-color brochure. Vitatron Medical, Inc., One Gateway Center, Newton, MA 02158. Vitatron Medical b.v., P.O. Box 76, NL6210 Dieren, The Netherlands.

*Over 10 years' service life expected under worst case conditions, 500 ohm load with 1.0 millisecond pulse duration; over 15 years with 0.5 ms duration.





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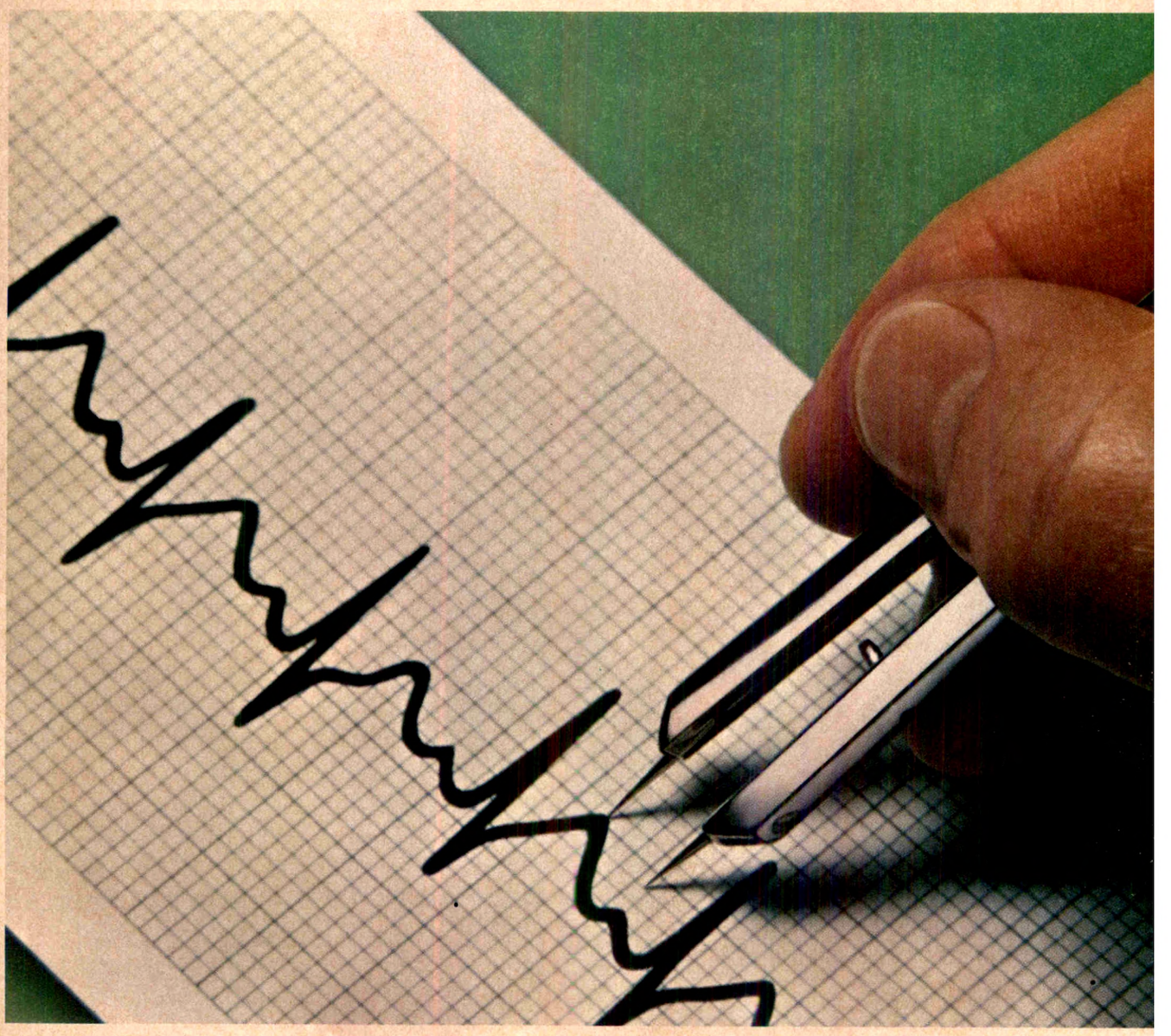
INDERAL®
(propranolol hydrochloride)
PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

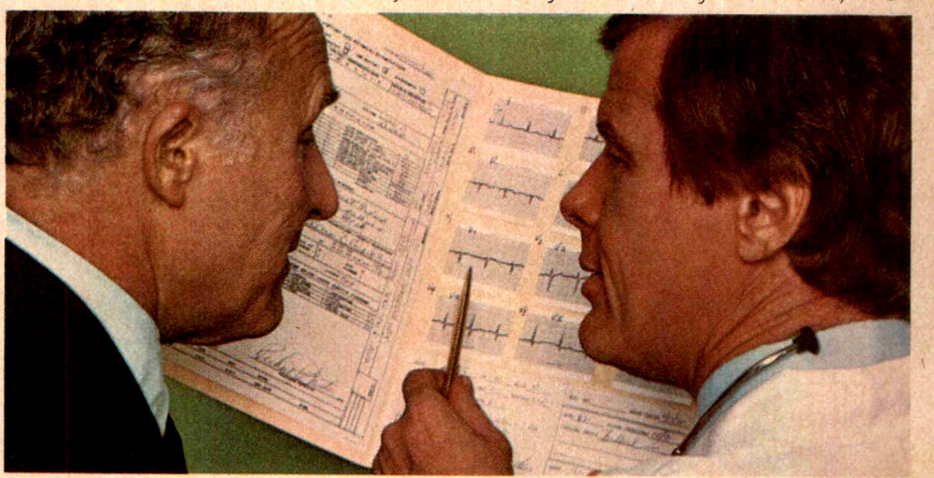
INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[8]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when



used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like* or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.

May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE:)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the signs of clinical developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.*, electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES: 1. Shand, D.G.: N. Engl. J. Med. *293*:280 (Aug. 7) 1975. 2. Conn, R.D.: Postgrad. Med. *55*(No. 2):131 (Feb.) 1974. 3. Fors, W.J., Vanderank, C.R., and Reynolds, E.W.: Am. J. Cardiol. *27*:190 (Feb.) 1971. 4. Levi, G.F., and Proto, C.: Cardiology *55*:249, 1970. 5. Stern, S.: Am. Heart J. *74*(No. 2):170 (Aug.) 1967. 6. Luria, M.H., Adelson, E.I., and Miller, A.J.: Circulation *34*:767 (Nov.) 1966. 7. Gianelly, R.E., Griffin, J.R., and Harrison, D.C.: Ann. Intern. Med. *66*:667 (Apr.) 1967. 8. Coodley, E.L., and Snyder, S.: Am. Fam. Physician *14*(No. 5):146 (Nov.) 1976. 9. Miller, R.R., Amsterdam, E.A., and Mason, D.T.: Drug Therapy *5*:110 (Feb.) 1975. 10. Danahy, D.T., and Aronow, W.S.: Postgrad. Med. *61*(No. 1):113 (Jan.) 1977. 11. Gettes, L.S.: Med. Opinion *5*(No. 9):19 (Sept.) 1976. 12. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 13. Michaelson, S.P., and Wolfson, S.: Cardiovasc. Med. *1*(No. 3):213 (Nov.) 1976. 14. Wit, A.L., Hoffman, B.F., and Rosen, M.R.: Am. Heart J. *90*(No. 5):665 (Nov.) 1975. 15. Bigger, J.T., and Giardina, E.G.V.: Cardiovasc. Clin. *6*(No. 2):103, 1974.

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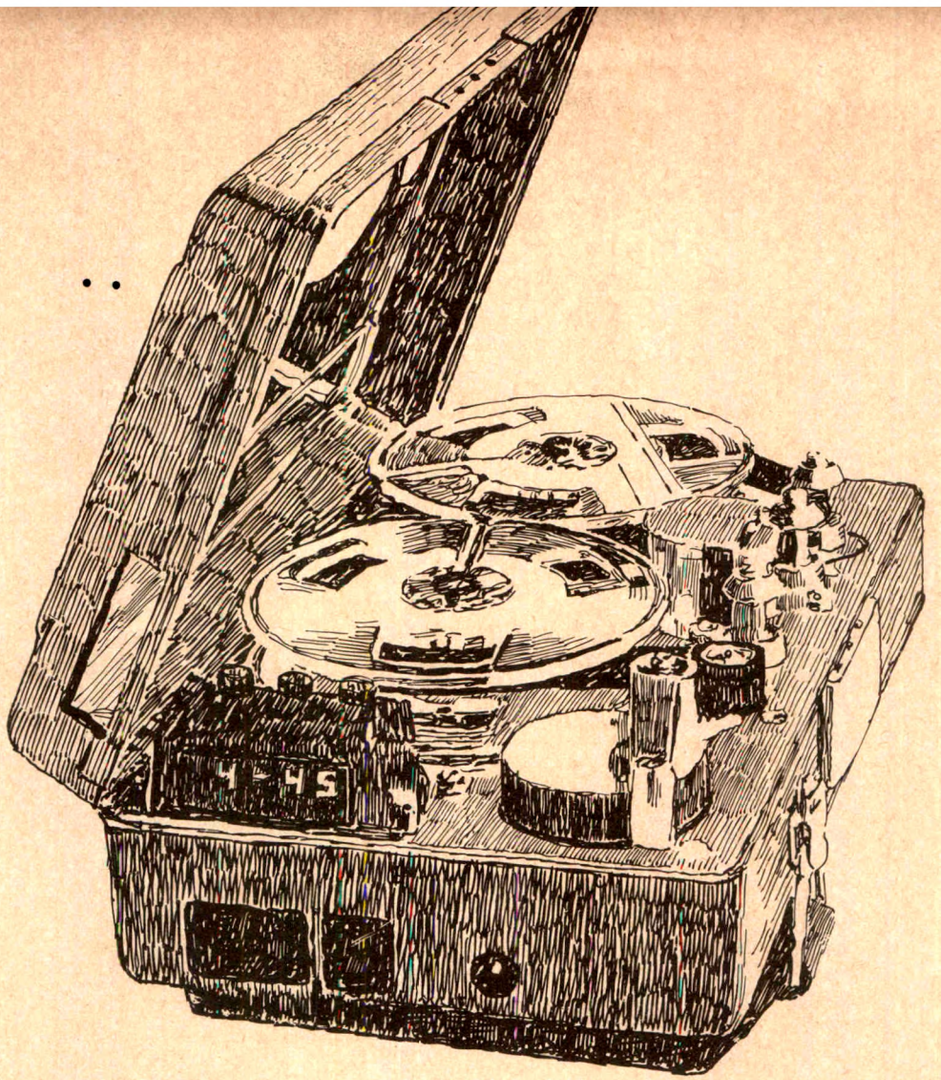

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**Clinical data available upon request.*

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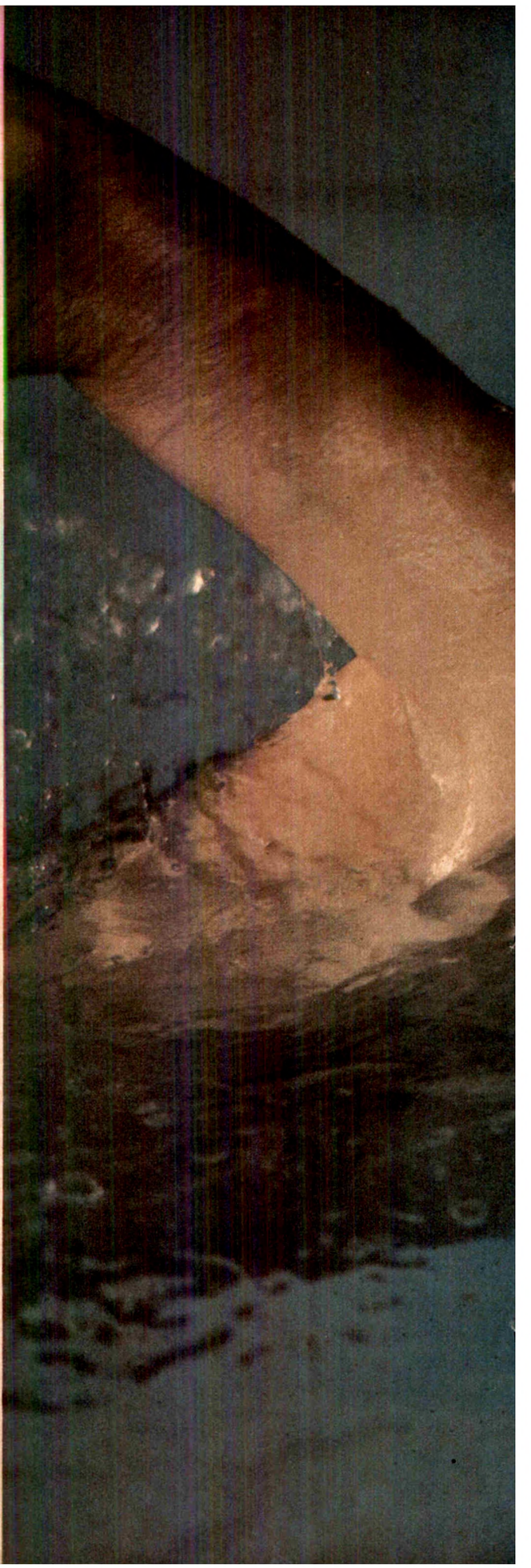

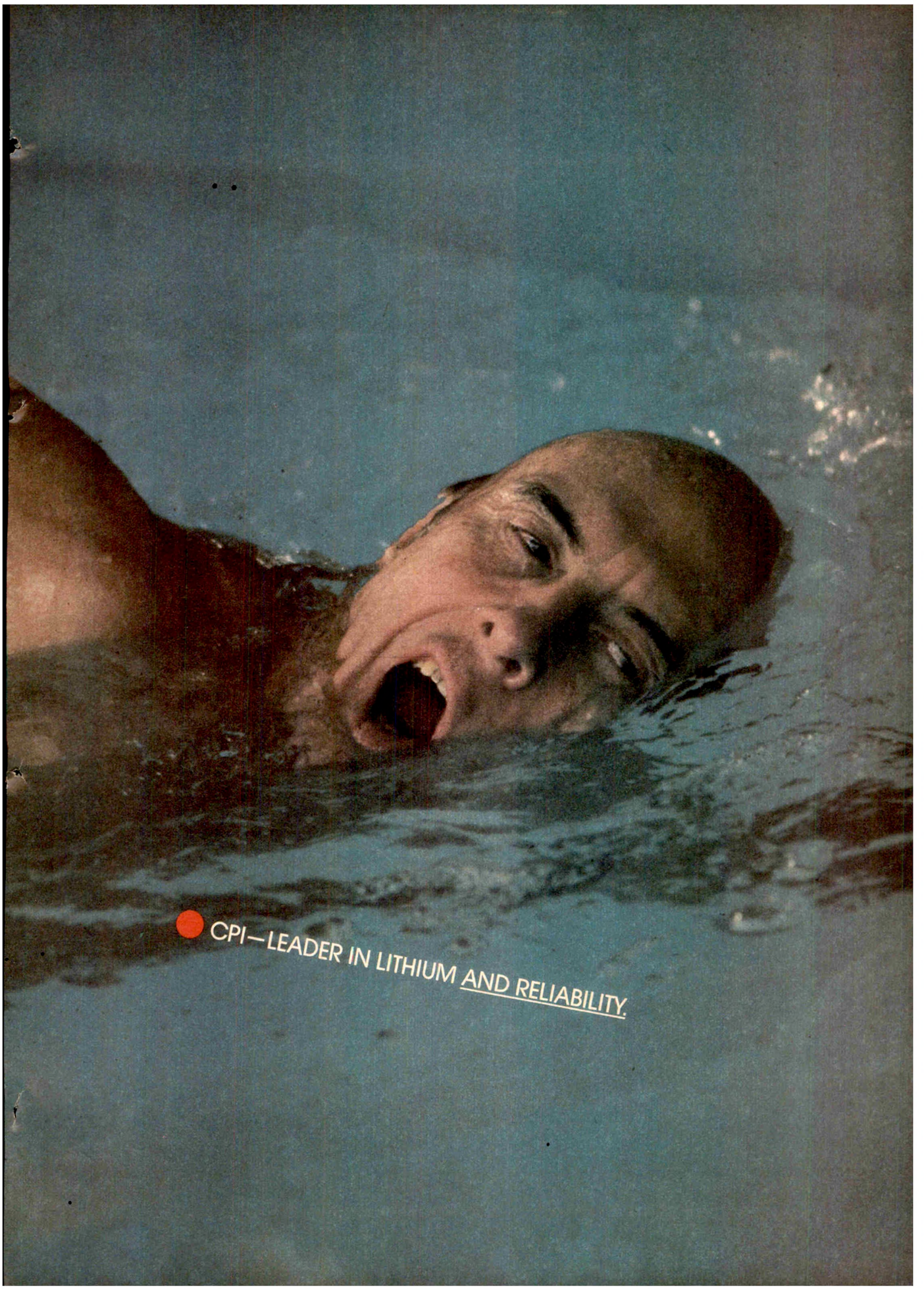
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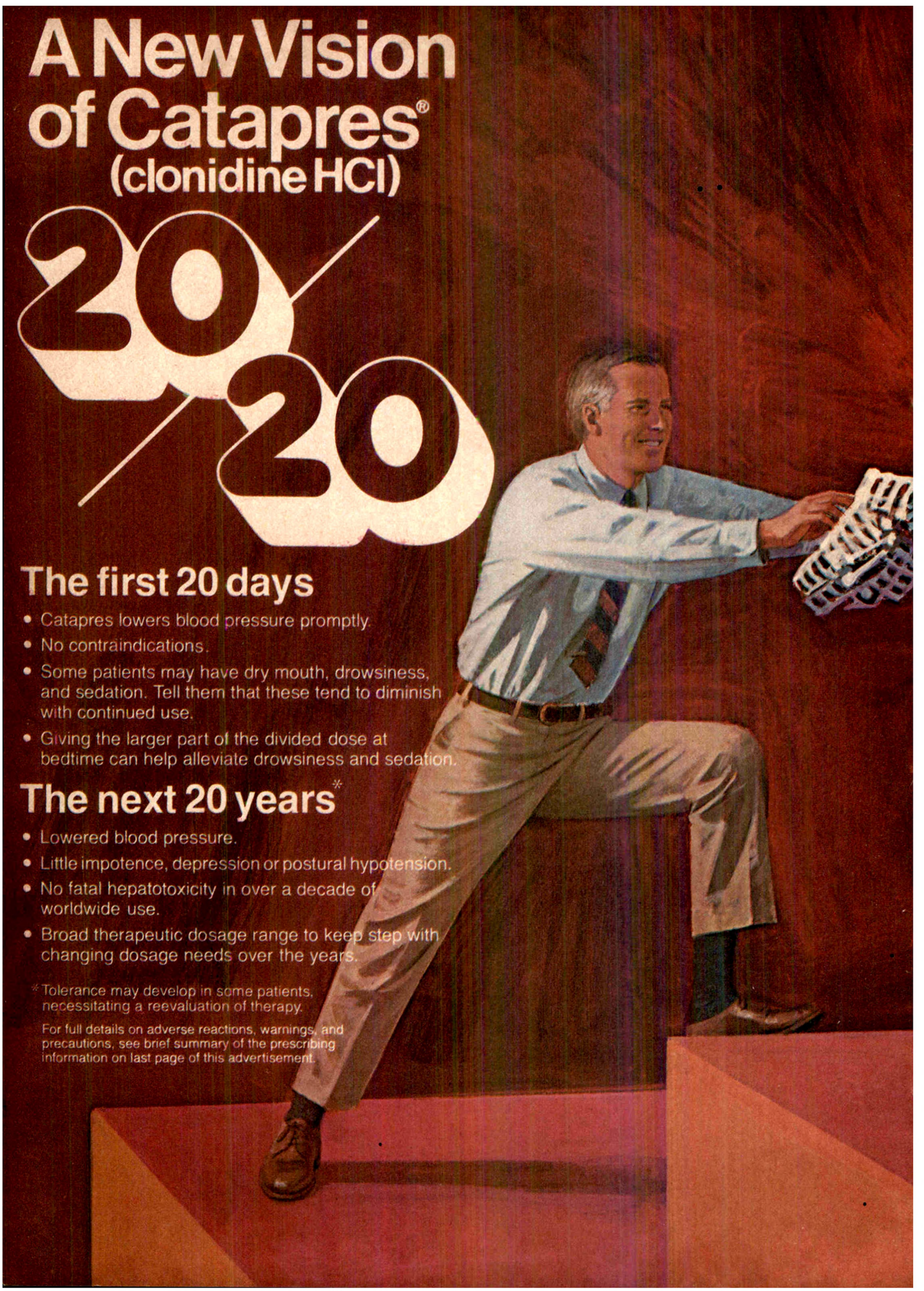
A New Vision of Catapres® (clonidine HCl)

20/20



The first 20 days

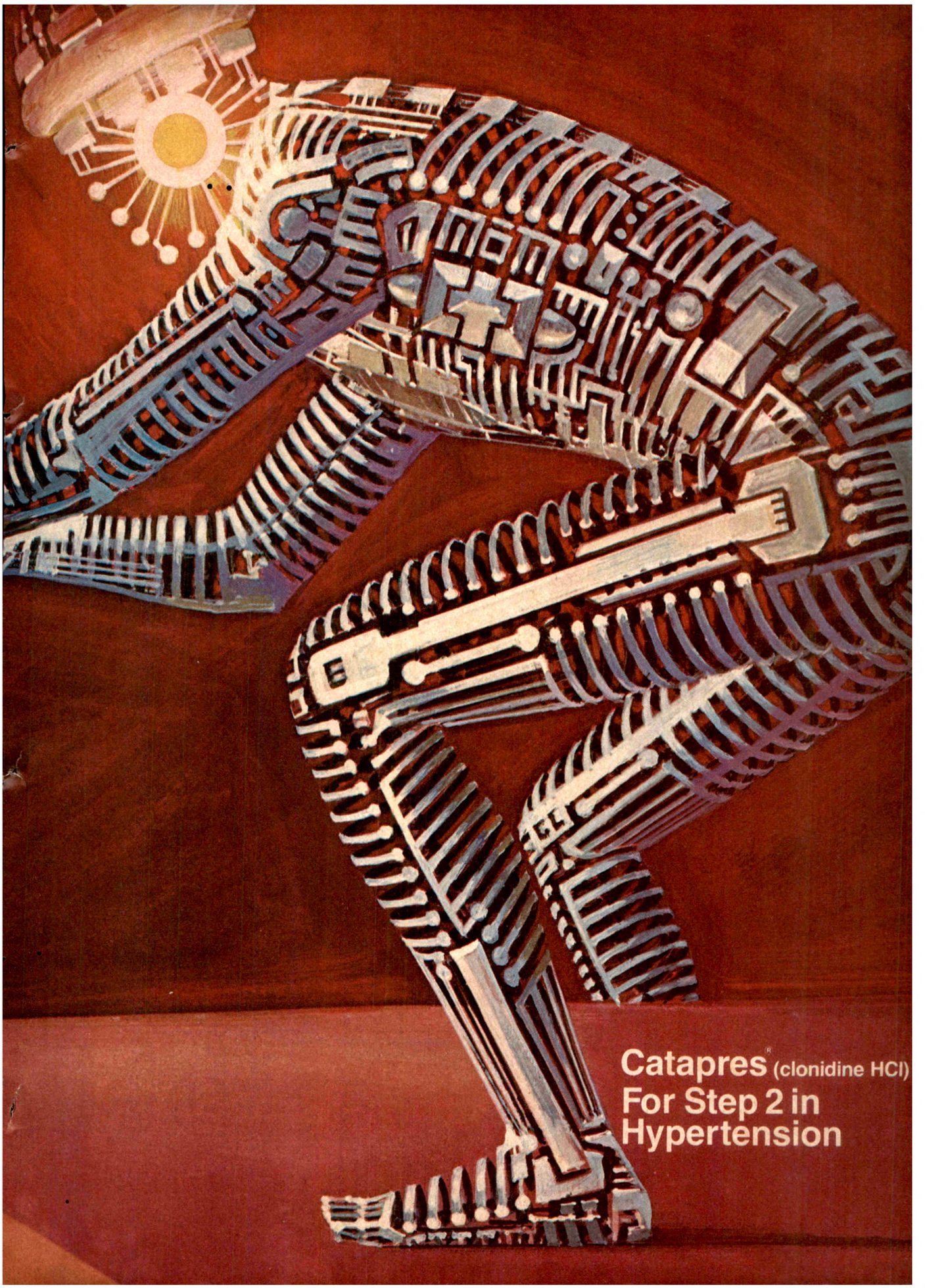
- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

The next 20 years*

- Lowered blood pressure.
- Little impotence, depression or postural hypotension.
- No fatal hepatotoxicity in over a decade of worldwide use.
- Broad therapeutic dosage range to keep step with changing dosage needs over the years.

* Tolerance may develop in some patients, necessitating a reevaluation of therapy.

For full details on adverse reactions, warnings, and precautions, see brief summary of the prescribing information on last page of this advertisement.

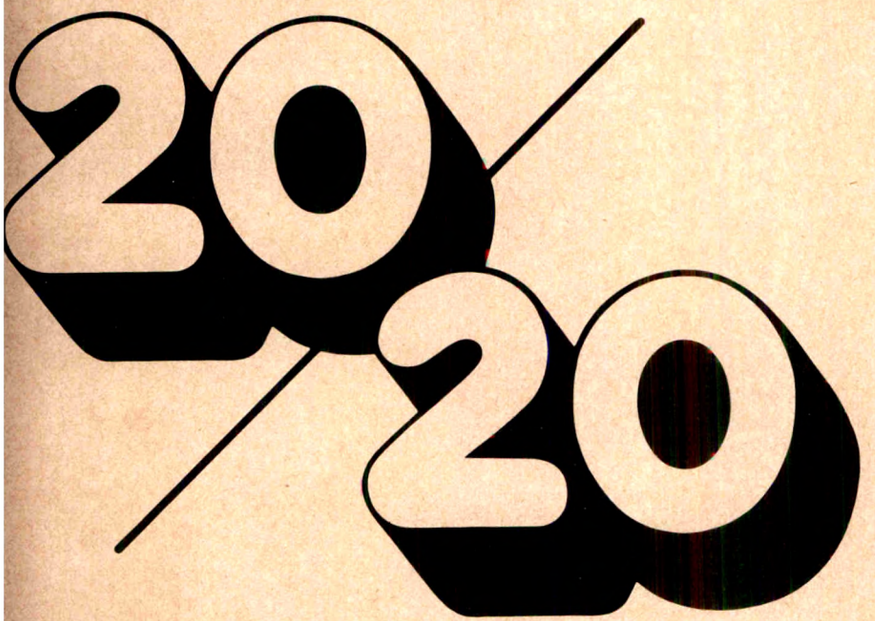

Catapres® (clonidine HCl)
For Step 2 in
Hypertension

HYPERTENSION

A New Vision of Catapres®

(clonidine HCl)

Tablets of 0.1 and 0.2 mg



What you do the first 20 days Can help him the next 20 years

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encepha lopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and menta depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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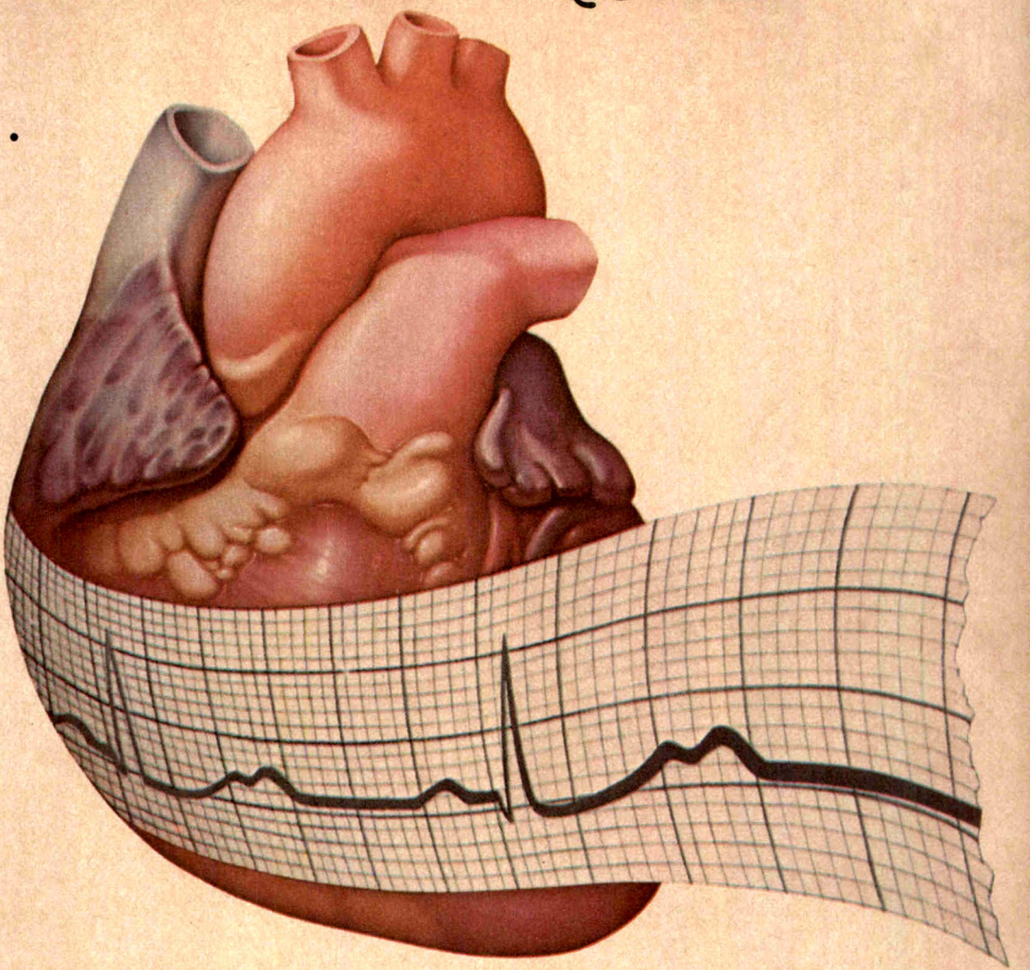
WHEN THERAPEUTIC DOSES OF POTASSIUM ARE REQUIRED:



CONVENIENT AND ECONOMICAL

KAON-CL 20%®

(potassium chloride) LIQUID

40 mEq per 15 ml

Indications: KAON-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. KAON-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: In patients with hyperkalemia, chronic renal failure, systemic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Warnings: Do not administer full strength. KAON-CL 20% will cause gastrointestinal irritation if administered undiluted.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: Nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effect is hyperkalemia (see Contraindications, Warnings and Overdosage).

Overdosage: If excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes. Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

How Supplied: Pints, gallons and 4 fl. oz.

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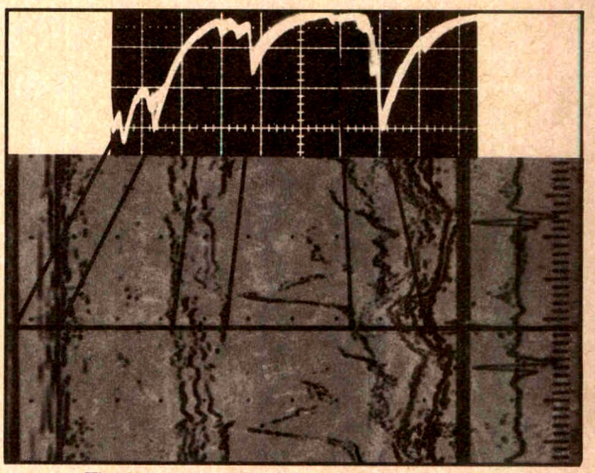

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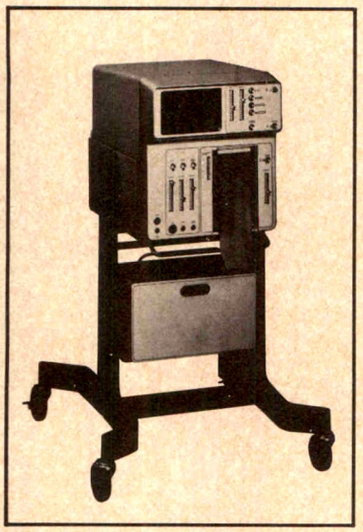

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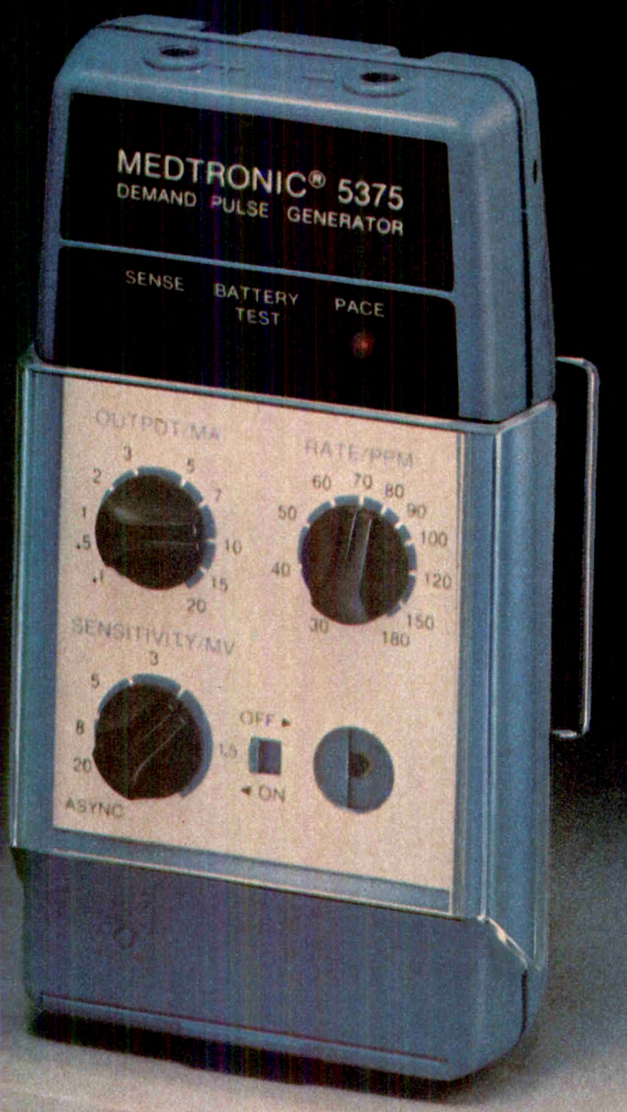

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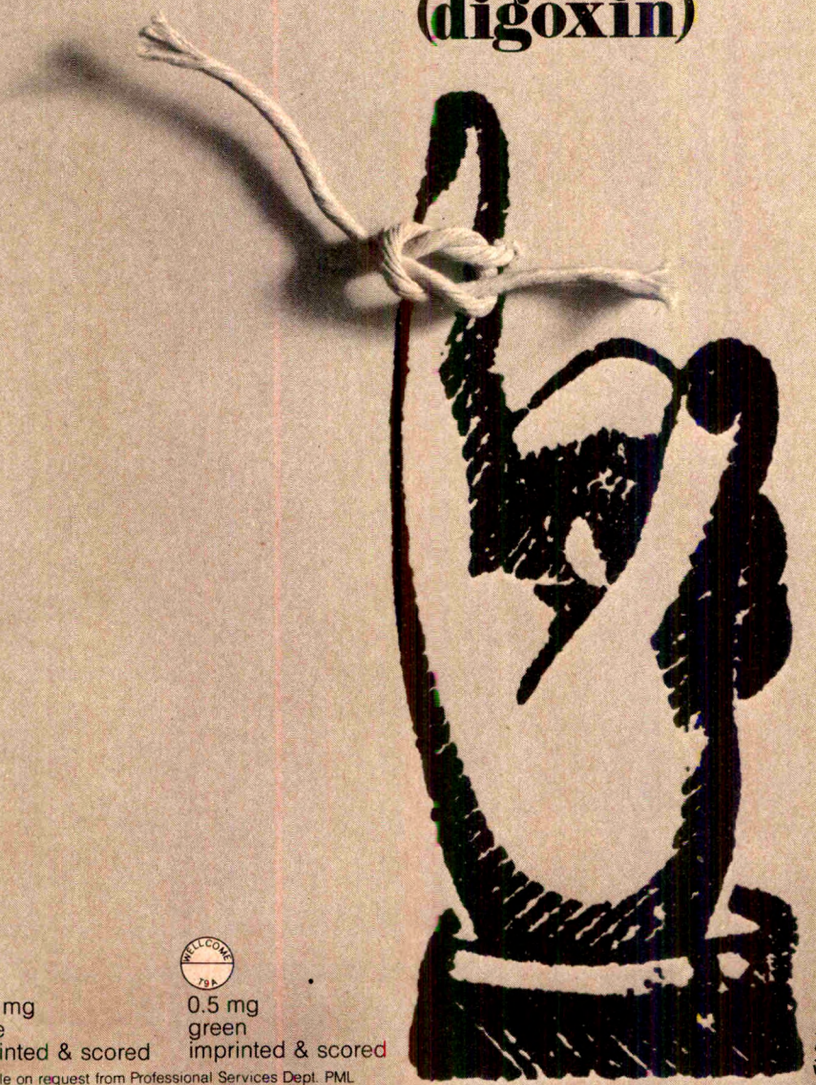

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CLINICAL STUDIES

Identification of High Risk Subsets Of Acute Myocardial Infarction

Derived from the Myocardial Infarction Research Units Cooperative Study Data Bank

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To identify the patient at high risk after acute myocardial infarction data on 400 patients obtained from the Myocardial Infarction Research Units Cooperative Data Bank were examined. Patients were grouped according to clinical findings as follows: uncomplicated (class I, 81 patients); mild to moderate failure (class II, 150 patients); severe failure with pulmonary edema (class III, 17 patients); and severe failure with shock (class IV, 152 patients). Hemodynamic data including pulmonary capillary wedge pressure and cardiac output were available in all patients. High risk subsets within clinical classes I, II and IV were identifiable. In class I, nonsurvivors had significantly ($P < 0.05$) higher values for pulmonary capillary wedge pressure (16 mm Hg) and heart rate (96 beats/min); nonsurvivors in class II also had a significant ($P < 0.01$) elevation in pulmonary capillary wedge pressure (23 mm Hg); and in class IV the high risk subset was characterized ($P < 0.01$) by pulmonary capillary wedge pressure (21 mm Hg), heart rate (100 beats/min), cardiac index (1.6 liters/min per m^2), stroke index (14 cc/m^2) and stroke work index (12 g-m/m^2). Discriminant function analysis using pulmonary capillary wedge pressure and heart rate predicted mortality in classes I to III with 72 percent accuracy; a similar equation representing stroke work index, pulmonary capillary wedge pressure and cardiac index had an 83 percent rate of accuracy in class IV patients. Interclass comparison of the last three measurements indicated that the data differed significantly among classes, thus signifying a spectrum of ventricular impairment after infarction that was commensurate with the clinical presentation. However, in individual patients the clinical examination did not consistently reflect the degree of ventricular dysfunction. Thus, careful bedside examination together with hemodynamic monitoring of wedge pressure, cardiac output and heart rate serve to identify the high risk patient after acute myocardial infarction.

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Hospital survival after acute myocardial infarction correlates with the degree of accompanying left ventricular dysfunction.[1–10] The presence and severity of ventricular failure, indicators of immediate prognosis, are currently assessed with careful bedside examination. In addition,

measurements of pulmonary capillary wedge pressure and cardiac output obtained in the coronary care unit have provided complementary objective information. Specifically, these hemodynamic data have been used to identify accurately the severely compromised ventricle and the associated poor prognosis.[1–7] However, prognostic features of increased risk in patients with lesser degrees of impairment after myocardial infarction have not been identified. In their early studies Peel et al.[8] and Norris et al.[9] suggested that age, sex, location of infarct, history of previous infarction, presence of systemic hypotension and clinical or radiographic evidence of pulmonary congestion and failure would provide such information. Yet, except for findings indicating obvious impaired performance, the relative contribution of these historical and clinical factors as objective criteria for predicting survival has not been substantiated.[2–5] Thus there is an obvious need to develop reliable prognostic criteria in such patients. In this investigation we reasoned that such criteria could be developed if a sufficiently large pool of clinical and hemodynamic data, representing the entire spectrum of ventricular dysfunction after myocardial infarction, were available for discriminant function analysis. This objective was realized by examining the data base for 400 patients who had been followed up in the nine Myocardial Infarction Research Units (MIRU).

Methods

Patient selection: Data were reviewed from 475 patients of whom 400 underwent hemodynamic evaluation. The data included information on 387 patients obtained from the Cooperative MIRU Data Bank and on an additional 88 patients from the University of Alabama MIRU seen between 1970 and 1972. The diagnosis of acute myocardial infarction was based on appropriate historical and clinical observations in association with documented electrocardiographic evidence of infarction. The evolution of diagnostic Q waves and S-T segment or T wave changes, or both, with associated serial enzyme alterations was required. The location of the infarction was documented electrocardiographically and was reported as anterior, inferior or lateral in location. Patients with S-T segment changes alone without accompanying Q waves were considered separately.

Patients were evaluated during the acute phase (less than 36 hours) of their infarction. Historical data relating to the presence and duration of angina, congestive heart failure, previous myocardial infarction and hypertension were available in 388 of the 400 patients. The patients were first characterized by clinical criteria on admission. The classification of Killip and Kimball[10] was used to represent the clinical estimate of ventricular dysfunction existing after infarction. The categorization was as follows: (1) Class I: Patients without auscultatory evidence of failure (pulmonary rales or third sound ventricular gallop, or both) were judged to have an uncomplicated infarction (81 patients). (2) Class II: The presence of basilar rales or ventricular gallop sound, or both, was judged to represent moderate ventricular failure (150 patients). (3) Class III: Pulmonary edema was reported for 17 patients. (4) Class IV: The diagnosis of shock was made in 152 patients. The criteria for shock, according to MIRU protocol, included both a systolic blood pressure of 90 mm Hg or less (or less than 110 mm Hg in patients known to have had hypertension previously) and clinical evidence of depressed mentation, pallor, cold and clammy skin and oliguria. Systemic blood pressure values were confirmed with arterial catheterization data. Patients with secondary causes of shock, such as arrhythmia with heart rates of 60 beats/min or less or 150 beats/min or more were excluded. Finally, information on mortality was limited to those deaths considered of cardiac origin.

Hemodynamics: After clinical categorization right heart and arterial catheterization was performed without preferential selection. Informed consent was obtained in all patients. Left ventricular filling pressure was estimated using pulmonary capillary wedge pressure. Cardiac output was measured with the dye-dilution or thermodilution technique. These 400 patients who underwent hemodynamic evaluation did not represent sequential admissions to the respective units or all patients observed in each unit. Their inclusion here was governed solely by the fact that their clinical and hemodynamic data were complete and available for analysis from the Data Bank.

From the hemodynamic data, left ventricular stroke work index (SWI, g-m/m^2) was calculated using the formula: SWI = (MSP − PCW) · SI · 0.0136 where MSP is calculated mean ejection pressure[11] and PCW is capillary wedge pressure (both in mm Hg), SI is stroke index (cc/m^2) and 0.0136 the conversion factor to metric units. Peripheral vascular resistance (PVR) (mm Hg/liter per min per m^2 or units) was calculated from the formula: PVR = (MSP − RAM)/CI where RAM is right atrial mean pressure (mm Hg) and CI the cardiac index (liters/min per m^2). In patients not having a reported right atrial mean pressure, peripheral vascular resistance was estimated as MSP/CI.

TABLE I

Interclass Comparisons of Hemodynamic Data*

Class	Patients (no.)	Pressures (mm Hg) SAP	DAP	MAP	RAM	PCW	HR	CI	SI	SWI	PVR
I	81	147 ±33	85 ±17	108 ±22	6 ±3	11 ±6	84 ±14	2.9 ±0.9	31 ±17	49 ±31	38 ±16
II	150	140 ±31	82 ±18	102 ±21	7 ±4	16 ±7	92 ±17	2.5 ±0.8	26 ±12	38 ±21	44 ±15
III	17	147 ±32	79 ±15	106 ±21	7 ±3	20 ±9	95 ±19	2.2 ±0.9	19 ±14	30 ±28	50 ±18
IV	152	95 ±16	63 ±12	73 ±12	12 ±7	20 ±7	97 ±19	1.8 ±0.7	18 ±12	17 ±13	45 ±24

* A composite representation of all hemodynamic variables and their mean value (±1 standard deviation) for each clinical class (criteria of Killip and Kimball[10]). The entire group of 152 class IV patients is included.

CI = cardiac index (liters/min per m^2); DAP = diastolic arterial pressure; HR = heart rate (beats/min); MAP = mean arterial pressure; PCW = pulmonary capillary wedge pressure; PVR = peripheral vascular resistance (units); RAM = right atrial mean pressure; SAP = systolic arterial pressure; SI = stroke index (cc/m^2); SWI = stroke work index (g-m/m^2).

TABLE II

Interclass Comparisons of Hemodynamic Data*

Class	Pressures (mm Hg) SAP	DAP	MAP	RAM	PCW	HR	CI	SI	SWI	PVR
I vs. II	NS	NS	0.05	0.05	0.01	0.01	0.02	0.05	0.01	0.01
I vs. III	NS	NS	NS	NS	0.01	0.01	0.01	0.01	0.05	0.01
I vs. IV	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02
II vs. III	NS	NS	NS	NS	0.05	NS	NS	0.05	NS	NS
II vs. IV	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.01	NS
III vs. IV	0.01	0.01	0.01	0.01	NS	NS	0.05	NS	0.01	NS

Statistical analysis of the hemodynamic data between each clinical class. Nonsignificant (NS) and statistically different ($P < 0.05$ or < 0.01) pairings are identified. Abbreviations as in Table I.

Statistical analysis: In addition to the assessment of clinical and hemodynamic data, sets of hemodynamic variables from all classes were compared individually and collectively using discriminant function analyses[12] to predict mortality. This method was used to derive a function that consisted of a linear combination of any chosen number of variables modified by statistically determined coefficients. Such an analysis permits a description of the specific influence of various measurements on overall survival and thereby an expression of prognosis. The utility of such an expression in predicting mortality has been previously demonstrated.[5,13] In this study, the variables analyzed in varying combinations were cardiac index; pulmonary capillary wedge pressure; heart rate; mean, diastolic and systolic arterial pressures; mean right atrial pressure, and peripheral vascular resistance. Solving the derived discriminant function with the required variables then resulted in a prediction of mortality for that patient. Information on radiographic heart size was not included in the data profile.

Results

Clinical and hemodynamic data: In classes I, II and III the clinical (age, sex and infarct location) and historical (previous infarction, angina, heart failure or hypertension) data had no statistical bearing on clinical outcome. In class IV, however, this information was found with significant ($P < 0.05$) frequency in nonsurvivors.

Class I: Eighty-one patients without clinical evidence of heart failure were grouped as having an uncomplicated infarction. Anterior infarction and inferior infarction were each observed in 44 percent; the remaining 12 percent had either S-T segment changes alone (9 percent) or lateral infarction (3 percent). The overall mean age was 56 years with men outnumbering women 6 to 1. The overall mortality rate was 10 percent.

Wedge pressure, cardiac index, stroke index and stroke work index averaged 11 mm Hg, 2.9 liters/min per m^2, 31 cc/m^2 and 49 g-m/m^2, respectively (Table I). As will become evident the interclass comparison of such information as wedge pressure, cardiac index and stroke work (Table II) indicates that as a whole class I patients (those without clinical evidence of heart failure) had a significantly higher level of left ventricular performance than patients in the other three classes. Left ventricular filling pressure and heart rate were significantly ($P < 0.05$) higher in class I nonsurvivors (16 mm Hg and 96/min, respectively) than in survivors (10 mm Hg and 83/min, respectively) (Table III). The other hemodynamic data did not distinguish this high risk

TABLE III

Intraclass Comparisons of Hemodynamic Data for Survivors and Nonsurvivors*

	Patients (no.)	Pressures (mm Hg) SAP	DAP	MAP	RAM	PCW	HR	CI	SI	SWI	PVR
Class I											
Lived	73	147 ±34	85 ±18	108 ±23	6 ±3	10 ±5	83 ±14	3.0 ±1.0	32 ±17	50 ±32	38 ±14
Died	8	143 ±14	83 ±11	107 ±6	8 ±4	16† ±9	96† ±18	3.0 ±1.2	25 ±16	39 ±26	51 ±30
Class II											
Lived	133	138 ±31	82 ±18	101 ±21	7 ±4	16 ±7	91 ±17	2.5 ±0.8	27 ±13	38 ±21	42 ±15
Died	17	155 ±31	90 ±12	114 ±17	12† ±4	23† ±6	98 ±19	2.3 ±0.5	25 ±7	37 ±16	51 ±14
Class III											
Lived	14	150 ±34	77 ±15	107 ±22	6 ±2	17 ±6	92 ±16	2.2 ±1.0	19 ±15	32 ±31	50 ±20
Died	3	131 ±8	87 ±11	100 ±6	9 ±5	25 ±12	113 ±26	1.9 ±0.4	17 ±5	23 ±11	53 ±10
Class IV‡											
Lived	32	98 ±9	65 ±9	75 ±7	9 ±3	15 ±7	89 ±20	2.4 ±0.8	28 ±14	28 ±15	35 ±11
Died	94	93 ±18	61 ±13	71 ±13	13† ±9	21†• ±6	100† ±18	1.6† ±0.6	14† ±9	12† ±8	50 ±29

* The intraclass comparisons of factors influencing survival. Patients who lived or died are identified in each clinical class. Variables and units are defined in text. Abbreviations as in Table I.
† Indicates statistical significance ($P < 0.05$) between nonsurvivors and survivors within each class.
‡ Patients with nonhypovolemic shock (right atrial mean pressure >5 mm Hg).

class I subset. The utility of this information in establishing prognosis by discriminant function is presented in a subsequent section (see later).

Class II: One hundred fifty patients were found to have a ventricular gallop sound or basilar rales, or both, and were therefore classified as having moderate heart failure. Fifty-nine percent had acute anterior and 38 percent had acute inferior infarction. Acute lateral infarction and isolated S-T segment changes were seen in 2 and 1 percent, respectively. The mean age was 58 years with an approximate male to female ratio of 4 to 1. The overall mortality rate was 11 percent.

The hemodynamic data for class II (Tables I and II) were consistent with a greater reduction of left ventricular performance than in class I ($P < 0.05$). Cardiac index, stroke index and wedge pressure averaged 2.5 liters/min per m^2, 26 cc/m^2 and 16 mm Hg, respectively. Mean cardiac index, stroke index and stroke work index in those class II patients who died averaged 2.3 liters/min per m^2, 25 cc/m^2 and 37 g-m/m^2, respectively. As in class I, mean wedge pressure in survivors was significantly lower ($P < 0.01$) than that of nonsurvivors (16 versus 23 mm Hg, respectively) (Table III). In addition, mean right atrial pressure was higher ($P < 0.01$) in nonsurvivors (12 mm Hg) than in patient survivors (7 mm Hg); however, mean heart rate was not significantly different. Arterial pressure, peripheral resistance, cardiac index, stroke index and stroke work index were of no value for the intraclass prediction of mortality. Class II patients demonstrated a greater degree of hemodynamic dysfunction than class I patients, but had less impairment than class III patients.

Class III: Pulmonary edema was reported for 17 patients. This limited number in all likelihood represents the inherent difficulty in obtaining adequate baseline hemodynamic information in patients with respiratory distress, instability and rapid fluctuations in clinical state. The incidence rate of anterior and inferior infarction was 79 and 14 percent, respectively; acute lateral infarction was seen in 7 percent. Men outnumbered women 2 to 1 and the average age was 65 years. The overall mortality rate for class III was 18 percent.

Mean values for cardiac index, stroke index and stroke work index in class III were all significantly lower ($P < 0.01$) (Tables I and III) than in class I. For the group, stroke index was reduced ($P < 0.05$) in comparison with class II whereas wedge pressure was higher than in class I or II. Nonsurvivors in this group could not be identified from hemodynamic criteria (Table III), but the small population sample prohibits meaningful statistical analyses and comparisons.

Class IV: By definition, patients in class IV had systemic hypotension and therefore arterial pressure in this group differed significantly from values in classes I, II and III. One hundred fifty-two patients constituted this group, which had an overall mortality rate of 70 percent. To determine whether any of these patients were volume-depleted a mean right atrial pressure of 5 mm Hg was arbitrarily chosen. Twenty-six patients judged to be hypovolemic on the basis of a mean right atrial pressure of 5 mm Hg or less were considered separately. Overall mortality for this hypovolemic subset was 48 percent. The remaining 126 patients with shock and a right atrial pressure greater than 5 mm Hg had a 75 percent mortality rate. These 126 patients are therefore considered to have primary shock and form the basis for all subsequent class IV analyses. Men outnumbered women 3 to 1 and the mean age was 59 years. Anterior infarction was seen in 57 percent and inferior infarction in 36 percent. S-T segment changes alone were reported in 5 percent and lateral infarction in 2 percent.

Hemodynamically, the patients with shock differed significantly ($P < 0.01$) from patients in classes I and II. Mean values for cardiac index, stroke index and stroke work index (1.8 liters/min per m^2, 18 cc/m^2 and 17 g-m/m^2, respectively) were all significantly lower whereas wedge pressure (20 mm Hg), heart rate and mean right atrial pressure were greater than the respective means observed in classes I and II. Within class IV, nonsurvivors could also be separated from survivors on the basis of these hemodynamic data (Table III). Specifically, cardiac index, stroke index and stroke work index were significantly lower and heart rate and wedge pressure higher ($P < 0.01$) in nonsurvivors. Class IV clearly represents the most profound functional impairment that exists after myocardial infarction.

Hemodynamic profile: The spectrum of ventricular dysfunction that exists after myocardial infarction within a given class or among classes could be represented by a comparison of cardiac index and left ventricular filling pressure or the three-dimensional display of stroke work index, cardiac index and filling pressure. For example, in Figure 1, cardiac index and filling pressure are presented for class IV with the additional considerations of infarct location and mortality. Patients with shock and a cardiac index of 2.0 liters/min per m^2 or less and wedge pressure of 15 mm Hg or greater had a 95 percent mortality rate. Patients in the other three hemodynamic quadrants had a substantially lower mortality rate. The respective mortality rates based on cardiac index (CI) and left ventricular filling pressure (LVFP) could be expressed as follows: CI less than 2.0 and LVFP less than 15, 55 percent; CI more than 2.0 and LVFP less than 15, 33 percent; and CI more than 2.0 and LVFP more than 15, 58 percent.

To characterize the hemodynamic profile for all 400 patients a series of averaged ventricular function curves (that is, stroke work versus filling pressure) calculated at several cardiac index levels was utilized. For each cardiac index level a curve was constructed by averaging work for three ranges of filling pressure (0 to 14, 15 to 25 and 26 to 40 mm Hg, respectively). The resultant work, cardiac index and filling pressure display is shown in Figure 2. The mean values ±1 standard deviation for each clinical class are shown in Table I. The expected biologic variability among the 400 patients accounts in part for the overlap among classes. However, the mean values for classes I, II and IV in which sample size was sufficient for statistically meaningful analysis differed ($P < 0.01$) from one another.

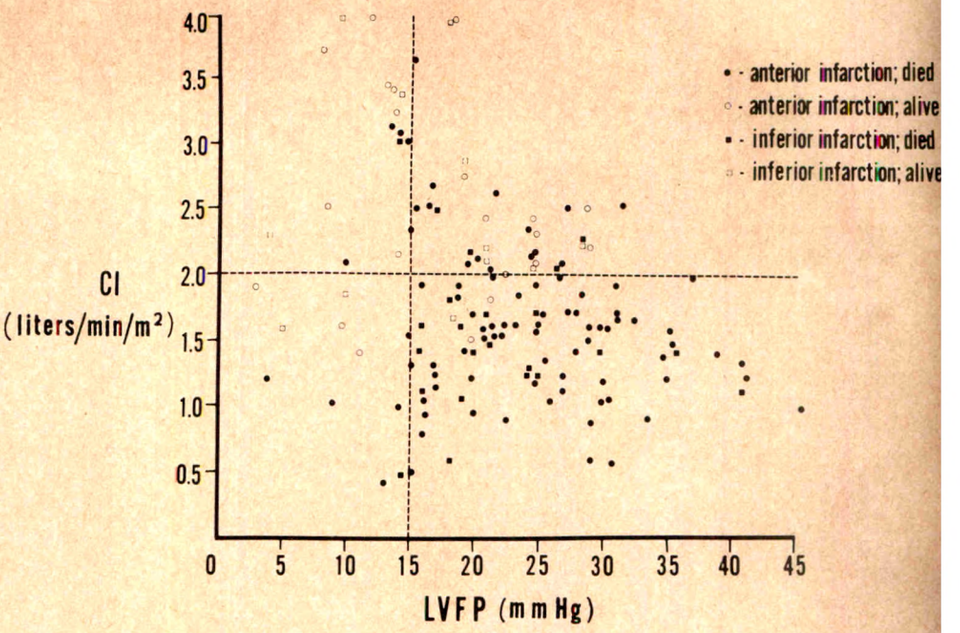

FIGURE 1. Class IV (shock) (152 patients). Identification of a high risk subset from the analysis of cardiac index (CI) and left ventricular filling pressures (LVFP). Infarct location and mortality are also represented.

Discriminant analysis: A discriminant function analysis (DF) can be used to weigh the influence of individual variables so as to predict mortality. A three variable discriminant analysis of stroke work index (SWI), cardiac index (CI) and wedge pressure (PCW) was developed for the 126 patients in shock. An 83 percent accuracy rate in predicting mortality was found. The resultant equation for these patients may be given as $DF_{1(Shock)} = 1.59 - 0.036SWI - 0.011CI + 0.023$ PCW where $DF_1 > 1.28$ indicates nonsurvival. Combining stroke work index, cardiac index and wedge pressure together with the infarct location did not improve prognostic accuracy. Other hemodynamic data, such as systolic, diastolic or mean arterial pressures, peripheral resistance and heart rate analyzed individually or in various combinations, were less useful in predicting mortality for class IV.

The observed mortality rate for classes I to III in our series ranged between 10 and 18 percent. In the individual patient, heart rate (HR) and wedge pressure (PCW) together provided an estimate of survival with a 72 percent accuracy rate. The resultant equation for the discriminant function (DF) using these two variables was as follows: $DF_{2(Failure)} = -0.568 + 0.018$ PCW $+ 0.005$ HR where DF_2 greater than 0.35 indicates nonsurvival. Moreover discriminant analysis using heart rate and wedge pressure together with age, infarct location, mean right atrial pressure, stroke index and stroke work or other hemodynamic data did not improve on the 72 percent accuracy rate obtained using heart rate and wedge pressure alone.

Discussion

Before we discuss the results of this investigation and its implications a number of comments are in order regarding the use of pooled data. The clinical and hemodynamic data base from which our study was derived represents retrospective information from the nine Myocardial Infarction Research Units. The appropriate historical and clinical definitions of acute infarction associated with electrocardiographic and enzymatic evidence of infarction were required. However, a common protocol dictating methodologic policy for hemodynamic data acquisition was not in effect. Thus cardiac output, for example, may have been measured with dye-dilution or thermodilution techniques. Information pertaining to specific techniques, reproducibility and the like may be obtained from an appropriate scientific publication of the individual units. We do not believe that such differences in technique would significantly hinder the interpretation of the information. Nevertheless, by its very nature certain constraints do exist with respect to the analysis of such pooled data. We have therefore made no attempt to single out similarities but rather only statistically significant differences. Moreover, this information obtained from a cross section of the U. S. medical centers does not represent sequential admissions. Thus it will not accurately reflect either the average experience of any given coronary care unit or the expected incidence of the various clinical categories of patients.

Clinical versus hemodynamic findings: In general, the scope of the clinical presentation appeared to follow the hemodynamic measurements of wedge pressure and cardiac index. Considered collectively, evidence of ventricular impairment or failure (that is, depressed cardiac output and elevated filling pressure) was accompanied by clinical findings of pulmonary rales or ventricular gallop sound, or both, for each clinical class. However, this agreement between clinical and hemodynamic observations was not consistent in the individual patient. This was particularly evident when

considering the high risk subset of classes I and II. Thus the degree of ventricular dysfunction in the individual patient and the prediction of hospital course after acute infarction could be more accurately assessed by complementing the clinical examination with hemodynamic monitoring. Clinical data on age, sex and infarct location were noncontributory in predicting mortality. Similarly, the presence or absence of historical information such as previous infarction, angina, failure or hypertension did not appear with distinguishing frequency in patients with an uncomplicated infarction or failure. However, these historical findings were present in the majority of nonsurvivors with shock.

Mortality rates for classes I and II: Role of left ventricular filling pressure: In general, the mortality rates observed in patients in classes I and II were in accord with the experience of others.[2–6,8–10,14,15] From this nationwide experience it is apparent that specific hemodynamic variables served to identify the high risk patient within each clinical class. Class I patients without auscultatory evidence of heart failure are considered to have a clinically "uncomplicated" infarction with minimal ventricular dysfunction. However, this is clearly not the case when complementary hemodynamic data are obtained. The range of filling pressure in these patients has been previously shown to be highly variable. For example, Hamosh and Cohn[3] observed a range of left ventricular end-diastolic pressure of 6 to 22 mm Hg (mean 15) in 14 patients without clinical evidence of failure and Wolk et al.[4] reported a mean of 16 ± 9 mm Hg for 23 similar patients. Additionally, filling pressure in our patients was closely related to early survival after myocardial infarction. Patients in class I not surviving hospitalization had significantly greater left ventricular filling pressures than their counterparts who survived. High risk patients with mild to moderate failure (class II) could also be distinguished by the level of filling pressure (23 mm Hg in nonsurvivors; 16 mm Hg in survivors). This observation represents a hitherto unstressed but very important observation in these class I and II patients. In addition, it emphasizes that the degree of myocardial impairment may be underestimated by the clinical examination. Heart rate also tended to be higher in nonsurvivors, a finding that reached statistical significance for class I.

Class III: Role of pulmonary edema: Because pulmonary edema (class III) was reported for only 17 patients, statistical conclusions on this group are limited and questionable. However, these patients differed hemodynamically from patients in classes I and II and had a higher mortality rate (18 percent). In 22 patients with pulmonary edema, Ramo et al.[1] reported that mean right atrial pressure, cardiac index and stroke index were 15 mm Hg, 1.9 liters/min per m^2 and 19 cc/m^2, respectively, and these values were significantly different from those of patients with lesser degrees of failure. However, a difference in such measurements between patients in classes III and IV could not be demonstrated. Sjogren[14] found that 15 of 40 patients (38 percent) who had frank pulmonary edema during the first 24 hours of their hospital stay died. Killip and Kimball[10] also reported a 38 percent mortality rate in 26 class III patients, whereas 17 percent of Scheinman's patients[15] with pulmonary edema after acute infarction expired.

Class IV: Role of stroke work index, cardiac index and wedge pressure in shock: Within the group with shock after acute mycardial infarction there is a subset at greater risk. These are the patients with a stroke work index of 20 g-m/m^2 or less, a cardiac index of 2.0 liters/min per m^2 or less and a wedge pressure of 15 mm Hg or greater. The observed mortality rate (96 percent) for this subset is consistent with previous observations[5]; however, these findings are only valid for patients with shock due to myocardial damage alone and do not include patients with other causes of hypotension, such as hypovolemia or arrhythmia.

Estimation of ventricular performance and contractile state after myocardial infarction: A hemodynamic profile of acute infarction was presented in 1973[5] for 79 patients followed up in the University of Alabama Myocardial Infarction Research Unit. This profile, which may be represented as the three-dimensional display of stroke work, cardiac output and filling pressure (Fig. 2) served also to describe the spectrum of left ventricular dysfunction for the 400 patients reported herein. Represented in this geometrical structure

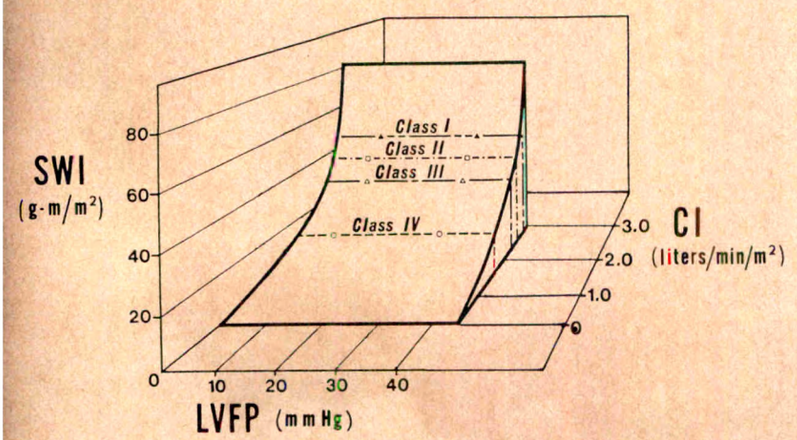

FIGURE 2. Hemodynamic profile of acute myocardial infarction based on stroke work index (SWI), cardiac index (CI) and left ventricular filling pressure (LVFP) presented for each clinical class.

are a series of ventricular function curves, a traditional estimate of pump performance relating to stroke work and filling pressure. On the basis of this information, the spectrum of stroke work index expressed with respect to the clinical classification could broadly be represented as follows: (1) uncomplicated infarction, greater than 40 g-m/m^2; (2) moderate failure, 30 to 40 g-m/m^2; (3) severe failure with pulmonary edema, 20 to 30 g-m/m^2, and (4) severe failure with shock, less than 20 g-m/m^2.

It is often assumed that myocardial contractile state can be assessed by determining the level of stroke work for any given series of filling volumes (or filling pressures). Unfortunately, in the individual patient this approach neglects the influence of arterial pressure on stroke volume as well as alterations in ventricular distensibility.[16] In the context of representing stroke work for each clinical class as we have here, it was assumed that the interplay of extrinsic and intrinsic factors regulating myocardial performance in any given heart had been assimilated. In physical terms ventricular work may be defined as the integral of the force-length loop. Because the ventricle shortens within the confines of its contractile state-dependent, maximal force-length relation,[16,17] a reduction in the slope of this relation will attenuate both the extent of wall shortening and work for any given condition of fiber length and load. Thus the progressive decline in stroke volume and work noted for classes I to IV, despite increments in filling pressure, suggests a continuous decline in contractile state that is reflected in the series of ventricular function curves. This spectrum of impairment probably represents the amount of accumulative muscle damage: That is, as the quantity of infarcted and ischemic myocardium increases there is a progressive reduction in contractile state whose functional limit is obtained for patients with shock.[5,18,19]

Clinical implications: Careful bedside examination together with measurement of heart rate and the hemodynamic determination of pulmonary capillary wedge pressure and cardiac output will identify the high risk subsets after acute myocardial infarction. It is in these patients that an aggressive, goal-oriented management program directed at reducing myocardial energy utilization must be instituted. The aim of this approach would be to control infarct size and reduce patient morbidity and mortality.

The high risk subsets among patients with acute myocardial infarction can be identified from the hemodynamic measurement of pulmonary capillary wedge pressure, cardiac output, stroke work and heart rate. Moreover it is possible to generate an expression of survival by discriminant function analysis for all patients on the basis of these data. This information will assist in the management of individual patients and will also permit evaluation and comparison of treatment programs and their influence on hospital survival.

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Coronary Anatomy and Arteriography in Patients With Unstable Angina Pectoris

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A prospective series of 188 patients with the syndrome of unstable angina pectoris undergoing coronary arteriography was reviewed to determine the spectrum of anatomic coronary artery disease, suitability for coronary revascularization and in-hospital morbidity and mortality. Thirty-two patients demonstrated normal to moderately diseased coronary arteries. None of these patients sustained myocardial infarction or died. Twenty patients (10.6 percent) had normal coronary arteriograms. Of the 156 patients having severe coronary artery disease (greater than 70 percent stenosis), 20 patients (13 percent) had left main coronary artery disease. One hundred forty-two patients (91 percent) were potential candidates for coronary surgery; 14 were not candidates because of distal vessel disease or poor left ventricular function. During cardiac angiography or in the subsequent hospital period 12 patients sustained a myocardial infarction and 7 of these died. Of these seven, six had left main coronary artery disease and one had three vessel disease. In three patients who died (1.9 percent of those with severe coronary artery disease) the death may have been related to cardiac catheterization because evidence of myocardial necrosis began within 24 hours of study. Thus, patients with the syndrome of unstable angina pectoris usually presented with severe coronary artery disease and were candidates for coronary revascularization. The anatomic severity of coronary artery disease appeared to be the most important factor contributing to myocardial infarction or death after cardiac catheterization. Mortality after catheterization was primarily associated with left main coronary artery disease.

Unstable angina pectoris is a clinical syndrome describing the patterns of ischemic chest pain interposed between acute myocardial infarction and chronic stable angina pectoris. Patients with this cardiac condition are at high risk for myocardial infarction and death.[1–39] However, some groups[6,14–16,18,30,31,34,38–40] have reported the short-term prognosis during the period of hospitalization to be benign. In an attempt to plan appropriate therapy for these patients, many physicians have recommended coronary arteriography as soon as feasible after exclusion of an acute myocardial infarction. Nevertheless, several difficulties face the clinician dealing with the syndrome of unstable angina pectoris. There are no uniform definitions or criteria for selection of patients. This problem is of critical importance because there are subgroups of unstable angina pectoris having greatly varying prognoses. Chahine[41] has discussed the difficulty of defining unstable angina pectoris with different prognoses. The clinical course of medically and surgically treated patients is still not clearly established. The risks of cardiac catheterization and left ventricular and coronary angiography are still controversial. In part, this results from lack of a clear definition of what constitutes a catheterization-related complication, that is, one occurring during catheterization or within a certain period after the procedure. As a means of examining

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TABLE I

Anatomic Subgroups and Clinical Characteristics

Coronary Anatomy (no. of diseased vessels)	Cases (no.)	Male/Female Ratio	Mean Age (yr)	Angina Profile (Chronic/ At rest*/ STΔ's)	Electrocardiogram (Normal/ Abnormal [Scar])
Group A	156	131/25	53.5	116/153/86	31/125(61)
Severe CAD (1 v = 49, 2 v = 52, 3 v = 35)	136	115/21	53	98/135/81	29/107(53)
Left main CAD (0 v† = 3, 1 v† = 3, 2 v† = 5, 3 v† = 9)	20	16/4	58	18/18/5	2/18(8)
Group B	32				
Normal	20	15/5	48	15/20/1	12/8(1?)
Mild-moderate CAD	12	8/4	54	10/11/1	2/10(1)

* Pain at rest often did not occur after hospitalization and, when it did, an electrocardiogram was sometimes not recorded during an episode.
† Number of diseased vessels other than left main coronary artery.
CAD = coronary artery disease; 0 v = no vessel, 1 v = one vessel, 2 v = two vessels, 3 v = three vessels; STΔ's = S-T segment changes with angina at rest.

these problems a large prospective series of patients presenting with the syndrome of unstable angina pectoris was analyzed. This report reviews the spectrum of coronary arterial anatomy, suitability for coronary revascularization surgery and the in-hospital morbidity and mortality in these patients.

Methods

Selection of patients: During a 3 year period, 188 patients with the clinical syndrome of unstable angina pectoris underwent diagnostic angiography to evaluate coronary arterial anatomy and left ventricular function. All patients were evaluated clinically by one of the cardiology faculty. Unstable angina pectoris in this study was defined as (1) recent onset of effort angina, (2) changing pattern of effort angina (increasing frequency, intensity or duration), and (3) angina at rest. In addition, these various patterns of chest pain must have developed within 3 months of hospitalization and were not mutually exclusive. All patients with recent onset of effort angina also had angina at rest or a changing pattern of effort angina. Generally, ischemic symptoms persisted 5 or more minutes and were accompanied by transient ST-T wave changes in the electrocardiogram in patients with severe coronary artery disease. Electrocardiographic changes during chest pain were not essential for inclusion in the study. S-T segment changes were not considered diagnostic of ischemia unless they were 1 mm or greater.

Patients with serious noncardiac illnesses, significant nonischemic heart disease or acute myocardial infarction were excluded from analysis. Patients presenting with the syndrome of unstable angina but not seen by one of us were also excluded. Myocardial infarction was excluded after an observation period of at least 24 but usually 48 to 96 hours. During this time, evidence for myocardial necrosis included an abnormal rise and fall of serum levels of glutamic oxaloacetic transaminase (SGOT), creatine kinase (CK) and lactic acid dehydrogenase (LDH) with its isoenzymes; or evolutionary S-T segment or Q wave changes, or both, in serial electrocardiograms. CK isoenzyme analyses were not available at our institution during the period of this study.

Initial treatment: Patients were treated initially with bed rest, isosorbide dinitrate and nitroglycerin sublingually. If patients were taking propranolol, the dose was reduced to 80 to 160 mg/day; otherwise administration of the drug was not begun until after cardiac catheterization.

Angiography: After the initial observation period, coronary arteriography was performed using the Judkins or Sones technique.[42,43] Because systemic heparinization of patients undergoing coronary arteriography did not become routine until after this study was begun, 34 (18 percent) of the total patient population did not receive heparin during cardiac catheterization. Selective coronary cineangiograms filmed at a rate of 60 frames/sec and large roll films at 2 to 6 frames/sec in multiple projections were available for definition of coronary arterial anatomy. Left ventricular biplane angiograms were obtained at a rate of 6 frames/sec after ventricular injection of 50 to 60 ml of sodium and meglumine diatrozoates.[44]

Candidates for saphenous vein bypass grafting: Patients were considered potential candidates for surgery if 70 to 100 percent obstruction of the luminal diameter of one or more coronary arteries was present without diffuse distal vessel disease or poor left ventricular function. Ventricular function was considered poor primarily on the basis of an ejection fraction of less than 0.30 or generalized hypokinesia, or both, as documented with left ventricular angiography. Unsuitability for coronary revascularization was determined jointly by a cardiologist and a cardiac surgeon.

Classification of coronary anatomy: Disease in the lumen of the major coronary arteries was classified as follows: (1) absent (normal coronary arteries)—less than 25 percent stenosis; (2) mild to moderate coronary artery disease—25 to less than 70 percent stenosis; (3) severe coronary artery disease—70 to 100 percent stenosis, and (4) left main coronary artery disease—greater than 50 percent stenosis.

Results

Spectrum of Coronary Artery Disease

Subgrouping: On the basis of coronary anatomy, 188 patients presenting with the syndrome of unstable angina pectoris were classified into two major groups (Table I). The mean age of the patients was 53 years. One hundred fifty-four patients (82 percent) were men and 34 were women. Patients with severe coronary artery disease were classified in Group A, which consisted of 156 patients, including 20 with left main coronary artery disease and 136 with severe coronary artery disease without significant involvement of the left main

coronary artery. Group B was composed of 32 patients with normal or mildly to moderately diseased coronary arteries, including 20 with a normal coronary arteriogram and 12 with mild to moderate coronary artery disease.

Severe coronary artery disease without significant left main coronary involvement (Table I): The mean age of these 136 patients was 53 years; 115 were men and 21 were women. Excluding 2 patients with left bundle branch block, 53 patients (40 percent) had electrocardiographic evidence of an old myocardial infarction. Twenty-nine patients (21 percent) had a normal electrocardiogram. All but one of the patients had angina at rest. Ninety-eight patients (72 percent) had a history of chronic angina (chest pain for more than 3 months) and two had a questionable history of chronic angina. One hundred twelve patients had chest pain in the hospital and 98 had an electrocardiogram taken during episodes of pain. With the exclusion of 2 patients who had a marked intraventricular conduction abnormality, 81 patients (83 percent) of those having an electrocardiogram during chest pain were documented to have transient ischemic S-T segment changes. The 136 patients with severe coronary artery disease without disease of the left main coronary artery were further classified into those with 70 to 100 percent stenosis of one, two or three vessels; 49 (36 percent) had one vessel disease, 52 (38 percent) had two vessel disease and 35 (26 percent) had three vessel disease. Thus, approximately two thirds of these patients had multivessel disease.

Left main coronary artery disease: Twenty of the 156 patients (13 percent) had greater than 50 percent stenosis of the left main coronary artery and 18 of these 20 demonstrated 70 percent or greater stenosis in this artery. The mean age for this group was 58 years; 16 were men and 4 were women. Eight patients (40 percent) had electrocardiographic evidence of old myocardial infarction. Two patients had a normal electrocardiogram. Eighteen patients had a history of chronic angina and 18 had a history of angina at rest. Among the 10 patients who had chest pain in the hospital, 8 had an electrocardiogram during pain. In five of these eight transient ischemic S-T segment changes were recorded during episodes of chest pain. The patients were then classified according to the number of severely involved vessels in addition to the left main coronary artery. Only 3 of the 20 had severe disease limited to the left main coronary artery; 3 had single vessel, 5 had two vessel and 9 had three vessel coronary artery disease in addition to the left main stenosis. Thus, a large majority of patients with left main coronary artery disease also had severe involvement of the remaining coronary arteries.

Normal coronary arteriograms: Twenty (10.6 percent) of 188 patients with unstable angina pectoris had a normal coronary arteriogram. The mean age of these patients was 48 years; 15 were men and 5 were women. All of the patients presented with a history of angina at rest that usually was prolonged and responded poorly to nitrates. Twelve patients had a normal electrocardiogram and eight had an abnormal electrocardiogram that in one suggested a remote myocardial infarction. Of the 13 patients who had an electrocardiogram recorded during chest pain, one was thought to have had ischemic S-T segment depression. Eighteen patients had one or more major risk factors; in the remaining patient the presence of risk factors was not known.

Candidates for Saphenous Vein Bypass Grafting

The 156 patients with severe coronary artery disease were analyzed according to suitability for saphenous vein bypass grafting as determined from coronary anatomy and left ventricular function (Table II). One hundred forty-two of the 156 patients (91 percent) were considered potential surgical candidates because they had one or more graftable vessels and adequate left ventricular function. However, 44 patients (28 percent) had single vessel disease and surgery was often not advised by their primary physicians. The condition of 14 (9 percent) of the patients was considered inoperable because of diffuse distal vessel disease or poor left ventricular function, or both.

In-Hospital Morbidity and Mortality

Incidence of major complications: Major in-hospital complications of these patients with unstable angina pectoris were myocardial infarction and death. There were no deaths or myocardial infarctions as a result of an arrhythmia at the time of cardiac catheterization. No patient sustained a cerebrovascular accident. Twelve of the 156 patients (7.7 percent) with severe coronary artery disease (Group A) sustained an acute myocardial infarction; five patients survived and

TABLE II

Candidacy for Saphenous Vein Bypass Grafting in 156 Patients With Severe Coronary Artery Disease

	Patients	Percent
Candidates for grafting	142	91
Single vessel disease	44	28
Multivessel disease	98	63
Noncandidates for grafting	14	9
Severe distal vessel disease	8	. . .
Poor left ventricular function	4	. . .
Both of above	2	. . .

TABLE III

In-Hospital Myocardial Infarction or Death, or Both

Anatomic Groups	Patients (no.) Total	AMI	Death
Group A	156	12 (7.7%)	7 (4.5%)
Severe CAD	136	6 (4.4%)	1 (0.7%)
Left main CAD	20	6 (30%)	6 (30%)
Group B	32	0	0
Normal	20	0	0
Mild-moderate CAD	12	0	0
Groups A + B	188	12 (6.4%)	7 (3.7%)

AMI = acute myocardial infarction; CAD = coronary artery disease.

seven died (Table III). No patient in Group B with normal to moderately diseased coronary arteries sustained an acute myocardial infarction or died.

Analysis of patients sustaining an acute myocardial infarction: In Table IV each of the patients sustaining an acute myocardial infarction in-hospital is analyzed according to severity of stenosis of major coronary arteries, onset of symptoms, survival and clinical characteristics. Of the seven patients who died, six had left main coronary artery disease and one had hypothyroidism and severe three vessel disease. Three patients had symptoms and evidence of myocardial infarction within hours of coronary angiography and died within 24 hours of the procedure. Two patients had a myocardial infarction after 24 hours and died within 48 hours. One patient had a myocardial infarction after 48 hours and died within 72 hours. The last patient had a myocardial infarction 11 days after cardiac catheterization and died on the 12th day. Each of the patients who died had prior stable angina for at least 2 years. Four of the seven patients had a history of a previous myocardial infarction with pathologic Q waves. One patient had a history of an old myocardial infarction with nonspecific ST-T wave abnormalities. Electrocardiograms in the two remaining patients also revealed nonspecific ST-T wave abnormalities.

Of the five patients surviving an acute myocardial infarction, three had symptoms and evidence of myocardial necrosis during or several hours after cardiac catheterization. One patient sustained a myocardial infarction 9 days after catheterization. All of these patients had a prior history of stable angina with recent onset of angina at rest and abnormal electrocardiograms. Three had a history of a previous myocardial infarction that was confirmed in two by pathologic Q waves; the third patient's electrocardiogram exhibited nondiagnostic ST-T wave abnormalities. Of the remaining two patients, one had left bundle branch block and the other had left ventricular hypertrophy. Thus, among 12 patients sustaining an acute myocardial infarction, symptoms and evidence of myocardial necrosis developed in 6 patients within 24 hours, in 3 patients from 24 to 48 hours and in 2 patients more than 72 hours after cardiac catheterization.

Discussion

In the spectrum of symptomatic coronary artery disease, the clinical syndrome of unstable angina pectoris is placed between stable angina pectoris and myocardial infarction. Fowler[45] proposed the term "unstable angina," but the condition has been variously labeled since its original description in 1937 by Sampson and Eliaser[1] and Feil.[2] Some of these designations include "preinfarctional angina,"[9] "acute coronary insufficiency,"[10] "impending myocardial infarction,"[3] "intermediate coronary syndrome,"[7] "status angiosus,"[12] "accelerated angina pectoris"[22] and "crescendo angina."

Studies of the natural history of unstable angina pectoris have indicated considerable variation in the incidence of myocardial infarction and death.[7,8,11–16,21–24,26–28,30–32,35–40] These discrepancies may be due to differences in definitions and criteria of selection of patients with unstable angina pectoris. In particular, the older reported studies suffer from a lack of angiographic documentation of the severity of coronary artery disease. Indeed, the natural history of angina pectoris has been shown by Bruschke,[46] Friesinger,[47] Reeves[48] and Oberman[49] and their co-workers to correlate more closely with coronary anatomy on angiography and left ventricular function than with clinical data or definitions alone. Our investigation provides information on coronary anatomy and left ventricular function in patients with unstable angina pectoris and its subgroups. Furthermore, these observations are related to in-hospital myocardial infarction and death and to suitability for coronary bypass surgery.

Unstable angina with normal coronary arteriogram: Of the patients presenting with the syndrome of

TABLE IV

Data on 12 Patients Who Had an In-Hospital Myocardial Infarction or Died, or Both

Case no.	Age (yr) & Sex	Coronary Stenosis*				Onset After Cath		Prior Angina	History of MI	ECG
		LM	LAD	LCx	RCA	Symptoms of MI	Death			
1	58F†	0	5	4	6	At cath	2 hr	3 yr	Yes	Scar
2	54M	4	4	4	4	3 hr	3 1/2 hr	3 1/2 yr	Yes	NDSTT
3	66M†	4	6	4	6	6 hr	9 hr	15 yr	No	Scar
4	66M†	5	4	5	4	27 3/4 hr	28 hr	7 1/3 yr	Yes	Scar
5	53F	5	4	0	6	36 hr	36 hr	4 1/2 yr	No	NDSTT
6	57M	6	6	6	3	58 hr	60 hr	2 yr	Yes	Scar
7	69M	3	4	4	6	11 days	12 days	2 1/2 yr	No	NDSTT
8	57M	0	4	0	1	At cath	. . .	1 yr	No	LBBB
9	53F	0	5	3	4	6 hr	. . .	7 yr	Yes	Scar
10	46F	0	6	3	6	7 hr	. . .	3/4 yr	Yes	Scar
11	57M	0	3	4	3	46 hr	. . .	4 yr	Yes	NDSTT
12	60F	0	5	4	6	9 days	. . .	1 yr	No	LVH

* Grading of stenosis: 0 = absent; 1 = <25 percent; 2 = 25 to <50 percent; 3 = 50 to <70 percent; 4 = 70 to <90 percent; 5 = 90 to 99 percent; 6 = 100%.

† Did not receive systemic heparin.

Cath = cardiac catheterization; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LCx = left circumflex coronary artery; LM = left main coronary artery; LVH = left ventricular hypertrophy; MI = myocardial infarction; NDSTT = nondiagnostic ST-T wave abnormalities; RCA = right coronary artery.

unstable angina pectoris, 10.6 percent had normal coronary arteriograms. Similar findings have been reported in other studies.[19,23,36,39,50–52] Review of anginal pattern, electrocardiograms and risk factors for atherosclerosis did not distinguish the individual patients with normal coronary arteriograms from those presenting with unstable angina pectoris and severe coronary artery disease. However, as a group, the former had a less typical history for angina pectoris and were more likely to have an electrocardiogram that was normal or lacked evidence of a previous myocardial infarction.

Left main coronary artery disease and mortality: An additional 10.6 percent of the patients with unstable angina pectoris had left main coronary artery disease. This finding is in agreement with data from other recent studies.[22,35,53–55] Ten percent of our patients with left main coronary artery disease were thought to have died as a result of cardiac catheterization because they had symptoms or evidence of myocardial necrosis within 24 hours of the procedure. This mortality rate seems excessive when compared with other experiences.[22,50,53,54,56–58] Possible reasons for our higher mortality rate are a small number of patients (20) for statistical analysis, lack of routine heparinization, myxedema in one of the two fatal cases and occurrence of both deaths during the earlier years of experience with coronary arteriography when present techniques were not uniformly used.

Of the patients with severe coronary artery disease, 91 percent were considered potential candidates for saphenous vein bypass grafting on the basis of one or more bypassable vessels and adequate left ventricular function. Thirty-one percent of the surgical candidates had single vessel disease. The primary physician often elected to treat these patients medically. In a group of 65 patients undergoing surgical treatment for unstable angina pectoris at our institution, there were no hospital deaths.[59]

Myocardial infarction and death related to cardiac catheterization: The in-hospital risks of myocardial infarction and death are related to the severity of coronary artery disease. All patients experiencing a serious complication had 70 percent or greater stenosis of the major coronary vessels. Myocardial infarction and death were attributed to cardiac angiography only when these complications developed within 24 hours of the procedure. Thus, 6 of 188 patients (3.2 percent) presenting with unstable angina may have sustained a myocardial infarction as a result of cardiac angiography that in three cases culminated in death (1.6 percent). Because no emergency coronary bypass procedure was performed no catheterization-related infarction or death would be considered a complication of surgery. In the first 65 patients undergoing coronary revascularization, there was an interval of 10.4 ± 2 days (mean ± standard error of the mean) between coronary arteriography and bypass surgery. There were no in-hospital deaths.[59] Intraaortic balloon pumping was not used during the period of this study.

Characteristics of high risk subgroup with unstable angina: Patients who sustained a myocardial infarction or died in the hospital had unstable angina that usually met the criteria of an extremely high risk subgroup of patients with "preinfarctional angina" described by Gazes et al.[21] or a subgroup with the "intermediate syndrome" described by Bertolasi et al.[36,37] The high risk subgroup of Gazes et al. had a 43 percent 1 year mortality rate. The subgroup of Bertolasi et al. with the "intermediate syndrome" treated medically had a 35 percent mortality rate after a mean follow-up period of 8.3 months[36] and a 46 percent mortality rate after a mean follow-up period of 32 months.[37] The main clinical features of patients in these extremely high risk subgroups were (1) prolonged episodes of angina at rest usually continuing in the hospital and responding poorly to nitrates, (2) transitory ST-T wave changes in the electrocardiogram during episodes of chest pain, and (3) usually a history of stable angina or a previous myocardial infarction, or both.

Implications: Several pertinent facts are apparent from these data on patients presenting with the clinical syndrome of unstable angina pectoris and undergoing cardiac catheterization and angiography. The patients usually have severe coronary artery disease and are potential surgical candidates. A significant percent have left main coronary artery disease but, equally important, a significant percent have normal coronary arteries. There may be an increased risk of myocardial infarction and death from coronary and left ventricular angiography as judged from symptoms or evidence of myocardial necrosis occurring in the first 24 hours after cardiac catheterization. Anatomic severity of coronary artery disease is the most important factor predisposing to myocardial infarction and death. In-hospital death in patients with unstable angina undergoing coronary arteriography occurs primarily in those with disease of the left main coronary artery.

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Tortuosity as an Index of the Age and Diameter Increase of Coronary Collateral Vessels in Patients After Acute Myocardial Infarction

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A possible correlation among increase in diameter, lengthening or tortuosity and age of bypassed obstruction was investigated in coronary arterial collateral vessels. In 35 autopsy patients with a myocardial infarct of known age, as determined from clinical history and pathologic demonstration of an infarct of consistent age in the distribution of an obstructed vessel, 140 collateral vessels were identified in postmortem arteriograms and measurements made of their diameter and tortuosity. Multivariable regression analyses showed that collateral diameter and tortuosity increase with greater time after the infarction. It is suggested that identification of tortuosity in a coronary vessel may provide an indication that it functions as a collateral channel and of the degree of its dilatation and the time it has been a collateral channel. The lengthening that produces tortuosity probably arises from the same relaxation of medial tension that induces dilatation as a result of increased blood flow.

Little is known about the morphology and time course of the development of the collateral circulation in human beings with occlusive coronary artery disease.[1,2] A major problem in the study of the development of human coronary arterial collateral vessels is the necessarily limited number of sequential observations that can be obtained in any one subject. The variability in collateral patterns among species makes studies of the time course of changes in caliber of the collateral channels in various animals of limited value in understanding the human situation.

We have noted while reviewing postmortem coronary arteriograms from patients with and without coronary atherosclerosis[3,4] and with coronary arterial occlusive lesions[5] that collateral vessels appeared not only to increase in diameter but also in length after myocardial infarction. Lengthening of such arteries, fixed at either end by their connections, produces a tortuosity of the vessel. The observation that collateral channels may be tortuous is not new. In 1762, William Hunter,[6] describing the features of the collateral vessels bypassing occluded arteries, stated: "Whatever distends, must at the same time, lengthen them, and thereby produce serpentine turns." In 1883, von Recklinghausen[7] noted that as collateral vessels carry more blood they become thicker and more tortuous. Although numerous studies have been performed on collateral vessels, especially coronary collateral vessels, in recent years little attention appears to have been given to tortuosity.

Although the age of infarction is not a precise index of age of coronary occlusion because most vessels have some narrowing before infarcts occur, it does provide an identifiable point when blood flow through the coronary artery was suddenly diminished and such a change should be a stimulus for collateral vessels. Using this general relation in this study,

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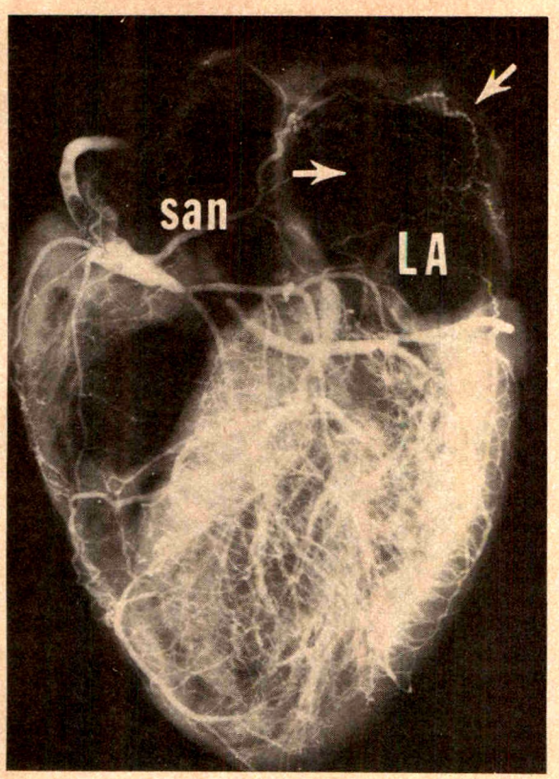

FIGURE 1. Postmortem coronary arteriogram of a patient with severe three vessel obstructive coronary atherosclerosis. The circulatory patterns are very complex, probably as a result of development of obstructive lesions of various ages. Note the dilated tortuous "corkscrew" collateral channels **(arrows)** traversing the left atrial (LA) wall. The sinoatrial nodal artery (san) is supplying blood to the distal right coronary and left circumflex arteries through the collateral channels.

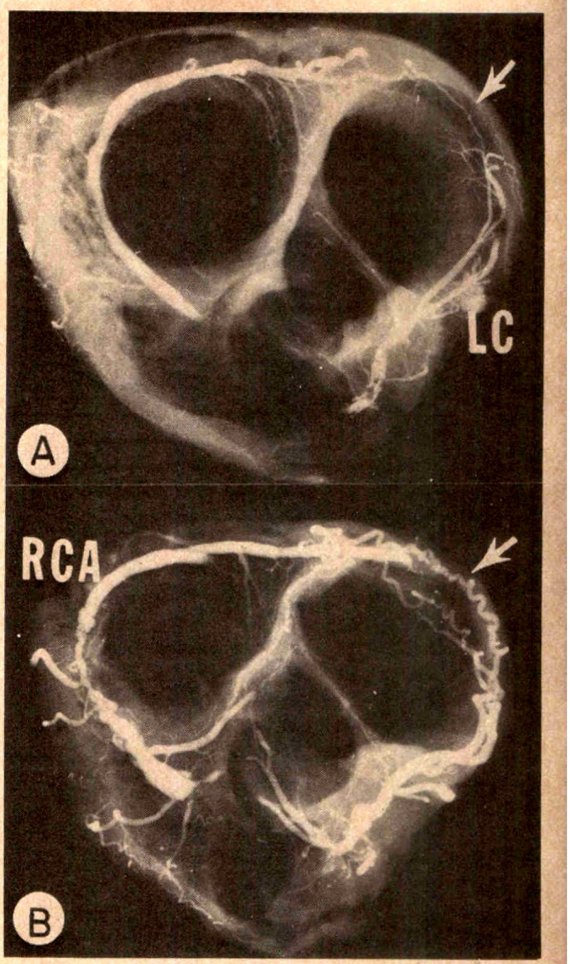

FIGURE 2. Collateral vessels **(arrows)** joining the left circumflex (LC and right coronary arteries (RCA). In these two hearts, the collatera vessels lie parallel to the plane of the radiograph and were suitable fo the measurements made in this study. **A,** the distal left circumfle coronary artery is filled from the right coronary artery. The myocardia infarct produced by coronary occlusion was 3 1/2 weeks of age. Th collateral channel is small in caliber and only slightly tortuous. **B,** th right coronary arterial obstruction had caused a myocardial infarct 1 years before death. The collateral channels filling the distal right cor onary artery from the left circumflex branch are large and markedl tortuous.

we have identified collateral bypass channels in the coronary vasculature of patients with occlusive coronary arterial lesions that produce myocardial infarcts of known age. The diameter and tortuosity of the collateral vessels were measured and compared with the patient's age, heart weight and age of occlusion for which the collateral channel was a bypass. The results show that tortuosity increases with the interval after myocardial infarction, the latter reflecting in part the time a vessel functions as a collateral channel.

Materials and Methods

Patients from the autopsy files of The Johns Hopkins Hospital were included in this study if they met the following criteria: (1) Their heart had been studied after coronary arteriography and fixation in distension.[8] (2) There was a total occlusion or significant (greater than 75%) obstruction of the luminal cross-sectional area of a major coronary artery with an associated myocardial infarct of known clinical age that was confirmed by pathologic study. Precise age of infarction was determined from a definite clinical history plus a pathologic demonstration of a myocardial infarct of consistent age as determined from gross and histologic features.[5] (3) One or more collateral vessels through which the coronary artery distal to the occlusion was being filled could be visualized in the plane of the postmortem arteriograms (Fig. 1 and 2).[1] Review of radiographs in multiple views and in stereoscopic projection allowed resolution of overlapping vessels. Collateral channels that ran obliquely to the plane of the radiograph were not included in the study.

Pathologic study: Coronary arteriography was performed in hearts obtained at autopsy by injection of a gelatin-pigment-barium mass with added formalin at pressures of 100 to 150 mm Hg controlled by manometer. The injection mass used is viscous and usually fills arterioles but not capillaries.[9] After completion of injection, hearts were fixed in distension with formalin at 20 to 40 cm water pressure introduced into the chambers through cannulas tied into the major vessels. Sets of stereoscopic radiographs were prepared on the intact heart and its transverse sections. The hearts were studied grossly and histologically for the presence of myocardial lesions and obstructive lesions of the coronary arteries. The

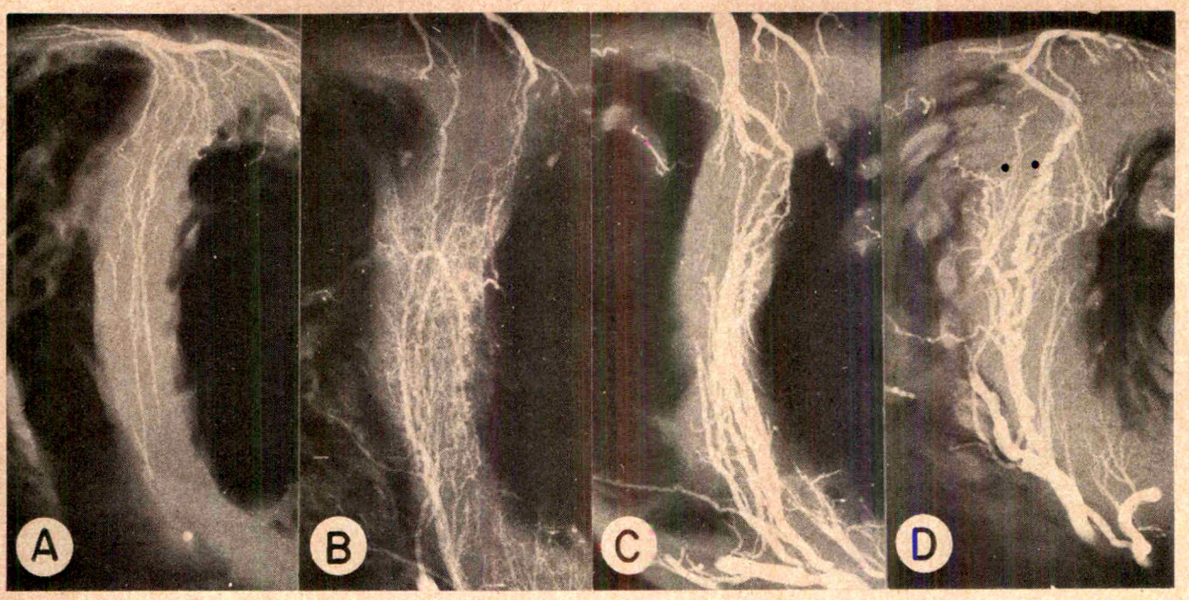

FIGURE 3. Series of radiographs of the interventricular septum of four hearts showing collateral channels bypassing coronary arterial obstructions of increasing age. Tortuosity (length) and dilatation increase with time. Numerous collateral vessels may be present at some stages but a few channels appear to become the preferred channel of flow. The most marked tortuosity is present in the mid part of the collateral. The radiographs are all oriented as in Figure 2 with the anterior interventricular septum toward the bottom and the left ventricle on the right side. In **A** and **C,** occlusions of the left anterior descending coronary artery had produced myocardial infarcts 3 days and 8 years, respectively, before death. The septal branches of the left anterior descending coronary artery are filled through collateral channels from the septal branches of the right posterior descending coronary artery. In **B** and **D,** proximal right coronary occlusions had produced infarcts in that vessel 9 days and 14 years, respectively, before death. The septal branches of the right posterior descending coronary artery are filled through collateral channels from the septal branches of the left anterior descending coronary artery.

pathologic findings were correlated with the clinical information in each case.

The diameter of collateral vessels was measured on the radiographs using an optical device with a scale calibrated to 0.1 mm. The diameter was determined from measurement of the mid portion of each collateral vessel and a representative diameter agreed upon by consensus among the observers[10] was ascertained. There was little intraobserver variability. The tortuosity of each collateral vessel was determined and expressed as cycles per centimeter by measuring the distance traveled, counting the number of wave cycles in that distance and dividing the number of cycles by the distance traveled. The cycles were counted from peak to peak. Cycle number was chosen and the amplitude of the waves and the three-dimensional excursions of the vessel were disregarded because of the difficulty and inaccuracy of determinations of each vessel length.

Statistical analysis: Data were obtained from measurements of collateral vessels, the patient's age, heart weight and the age of the coronary arterial occlusion associated with the collateral circulation as determined from the clinical history of the myocardial infarct confirmed with pathologic study. The facilities of The Johns Hopkins University Computer Center were used to carry out multivariable regression analysis using Biomedical Computer Program BMD02R.[11]

Results

Among the 980 autopsy patients whose heart had been studied after coronary arteriography and fixation in distension there were 35 hearts with 140 collateral vessels that had the proper orientation on the arteriograms for performing the measurements made in this study. The patients ranged in age from 35 to 86 years (average 65). The period of survival after the myocardial infarct, of which the causative coronary arterial obstruction was the subject of study, ranged from 2 days to 16 years. The heart weights ranged from 320 to 960 g (average 530).

In the 35 hearts 21 of the obstructive lesions being bypassed by the collateral vessels were total occlusions. The remaining 14 coronary lesions were obstructions of 75 to 99 percent of the luminal cross-sectional area. Percent luminal narrowing was estimated visually by comparing transverse sections of coronary arteries with a standard chart of measured reductions of luminal area. The 140 collateral channels identified ranged from 0.7 to 8.2 cm in linear distance from point of origin to termination. The diameter of the collateral vessels ranged from 0.2 to 1.6 mm.

Sequence of changes in collateral flow: The impression was gained from review of the arteriograms that in the early stages after acute myocardial infarction a number of channels dilate, function as collateral vessels and become tortuous. With passage of time a few collateral channels appear to be selected as preferential channels of flow and undergo further dilatation and tortuosity. The apparent sequence of changes in collateral flow through the vascular bed of the interventricular septum is illustrated in Figure 3. Inspection of angiograms also shows that in the entire course of the collateral channel between two larger arteries the greatest tortuosity occurs in its mid portion. The mid part of the collateral vessel is the portion that would undergo the greatest dilatation because the proximal

TABLE I

Mean ± Standard Deviation and Range of the Variables Studied in 140 Coronary Collateral Vessels in 35 Patients

Logarithmic heart weight (g)	2.725 ± 0.126 (2.505–2.971)
Age (yr)	65.1 ± 9.7 (35–86)
Diameter (D) (mm)	0.65 ± 0.28 (0.2–1.6)
Logarithmic age of infarction (yr)	−0.076 ± 1.008 (−2.301–1.204)
ν (cycles/cm)	3.28 ± 2.63 (0–15.7)

TABLE II

Correlation Matrix for Variables in 140 Collateral Vessels

	Age of Patient	Diameter of Collateral Vessel	Logarithmic Age of Infarction	ν
Log heart weight	−0.304	0.058	−0.082	−0.056
Age of patient		−0.124	0.076	0.150
Diameter of collateral			0.290	−0.353
Logarithmic age of infarction				0.220

and distal ends would be larger vessels arising from the supplying and supplied arteries.

Relations among collateral tortuosity, heart weight, age of infarction, patient's age and collateral diameter: Relations were sought among collateral tortuosity, age of infarction, heart weight, patient's age and collateral diameter. The logarithmic values of heart weight and age of occlusion were chosen to simplify graphic representation of the data (Table I). Correlation coefficients of these variables are shown in Table II. An equation predicting tortuosity of the collateral vessel from heart weight, age of infarction, collateral diameter and patient's age and equations predicting age of infarction and collateral diameter from the other variables were calculated using multivariate regression analysis. The program[9] makes predictive formulas by choosing from up to 99 variables in the sequence of their F values for inclusion. It begins by fitting a linear regression to the data and then adds single terms to the simple regression, obtaining a multivariate correlation coefficient for each step. Only statistically significant ($P < 0.05$) variables are entered into the equation as determined by the F value to enter. All variables were assigned a free status, allowing the program freedom to choose only those of significance for entrance into the formulas.

The formulas (Table III) show that collateral tortuosity may be predicted by age of infarction and diameter of collateral vessel. The older the infarct, the more tortuous the collateral channels. The larger the vessel, the less the tortuosity and the fewer cycles per centimeter it will have. The predictive formula obtained for logarithmic age of infarction illustrated a correlation with collateral caliber and tortuosity. Collateral vessels bypassing infarcts and presumably older occlusions are more tortuous and of larger caliber. The diameter of the collateral vessel is predicted from the age of the infarct with which it is associated, except that the caliber will be less the greater the number of cycles per centimeter found. The reduction of tortuosity expressed as cycles per centimeter in larger vessels simply reflects their lesser ability to accommodate reversals of direction within a given net distance traveled.

Discussion

Mode of formation and growth of collateral vessels: With the onset of occlusion of an epicardial coronary artery, those channels in communication between the distal nonperfused artery and adjacent arteries will have a pressure gradient favoring flow into the vessel distal to the obstruction, as shown in animal experiments.[1,2] It has been suggested that the dilatation of a vessel that occurs with an increase in flow is a result of increase in the shear stress on the endothelium.[12] This endothelial shear stress may induce local relaxation of medial smooth muscle and dilate the vessel. Dilatation continues until the drag on the endothelium returns to its control value. Once shear stress is diminished, the vessel wall regains its normal state of tension. Subsequently complete anatomic reorganization around the dilated caliber occurs, as indicated experimentally in dogs by an increase in mitotic activity of both the endothelial and smooth muscle cells in the coronary collateral channels.[13] Similar observations after experimental vascular interruption in the collateral fields of the rat mesentery[14] have shown that the most constant and progressive changes were increased diameter and tortuosity. It seems likely that a similar postocclusive dilatation and lengthening of the collateral beds stimulates the proliferation of collateral vessels in human beings as well. In man, however, unlike dogs and other experimental animals, the native collateral vessels

TABLE III

Multivariable Regression Formulas for Prediction of Tortuosity (ν), Age of Infarction and Diameter in 140 Collateral Vessels

Formula Using Statistically Significant ($P < 0.05$) Variables	Multiple Correlation Coefficient	SEE	F to Enter or Remove: Logarithmic Heart Weight	ν	D	Logarithmic Age of Infarction	Age of Patient
ν = 6.04 − 4.20 D + 0.92 logarithmic age of infarction	0.49	2.81	0.07†	. . .	19.61*	20.46*	0.83†
Logarithmic age of infarction = −1.49 + 1.49 D + 0.14 ν	0.45	0.91	0.77†	19.13*	27.30*	. . .	0.45†
Diameter = 0.81 + 0.11 logarithmic age of infarction − 0.05 ν	0.52	0.25	0.32†	19.61*	. . .	26.57*	1.49†

* $P < 0.001$.
† Not statistically significant ($P > 0.05$).
D = diameter; ν = cycles/cm; SEE = standard error of estimate.

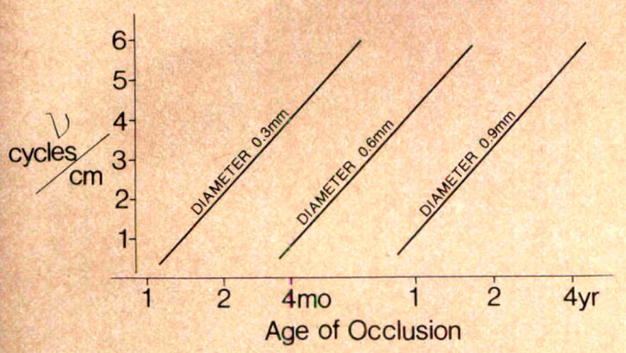

FIGURE 4. Diagram of the relation between age of infarction and tortuosity for collateral vessels of different observed diameters. ν represents tortuosity according to cycles per centimeter.

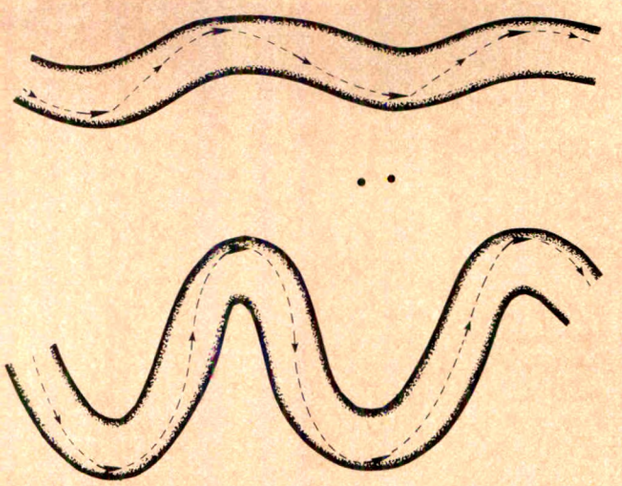

FIGURE 5. Diagram of the shift in the axial stream of most rapid flow as a result of increased tortuosity. As a result of the change in direction of flow at the peaks of the curves the flow impinges on the outer wall and tends to elongate the intervening straight segments between the bends.

do not appear to be substantial,[1] and actual vascular growth in response to arterial occlusion is of even greater significance.

Correlation of age of infarction and tortuosity and caliber of collateral vessels: The relation between age of infarction and the tortuosity and caliber of collaterals found in our study is shown diagrammatically in Figure 4. If, as suggested, the dilatation of collateral vessels is caused by relaxation of the medial smooth muscle as a direct consequence of increased flow related to occlusion, then the concomitant increase in length of the vessel must also result from proliferation of vessel wall. The increased length is seen as tortuosity because the ends of the vessels are fixed. The development of tortuosity may initially be an accentuation of deviations from a perfectly straight course. As the vessel bends, the axial stream deviates from the mid line (Fig. 5) and, as it impinges on first one wall and then another, would tend to lengthen the intervening segment of relaxed dilating vessel. The constraints of the surrounding tissue, and diverging course of branch vessels would constrain the excursions and force the vessel to acquire new cycles as well as to lengthen the existing ones.

Limitations of study: Although we believe it essential to study collateral vessels, which are species-variable, in patients with atherosclerosis, there are some inherent limitations to this approach to human collateral channels. Because it is impossible to determine the time course of the development of coronary arterial narrowings, which undoubtedly occur over a long period of time, we have used the age of infarction as a readily identifiable event, confirmable at autopsy, when coronary flow was suddenly and drastically impaired. Because this latter event should be a stimulus for collateral development, the data collected in our study have been interpreted as though collateral vessels began to function with the onset of the clinically datable occlusion that caused a myocardial infarct. It is probable that some collateral development was already present and would have been influenced by the duration and degree of obstruction in the coronary arteries preceding the onset of the clinical infarction. Another factor that we were not able to take into account is the distribution and severity of atherosclerosis in the entire coronary arterial bed, which may also influence the development of collateral vessels. For example, the complex pattern of collateral filling shown in the heart in Figure 1 is probably attributable to the severe three vessel disease with obstructive lesions of various ages.

Vascular reactivity of collateral vessels: Despite these limitations, the age of infarction does appear to vary directly with collateral size and tortuosity. Furthermore, the time course of collateral development identified here is compatible with clinical observations at angiography. In our study new vessels comparable in caliber with smaller epicardial coronary arteries formed within 6 months, and this finding is compatible with the reports of Fam and McGregor[15] that the greatest improvement in collateral function after administration of nitroglycerin occurred in patients with ischemic symptoms for more than 6 months. Vascular remodeling is probably of importance in the development of nitroglycerin responsiveness. It has been shown that collateral vessels in patients without coronary disease are largely unresponsive to nitroglycerin.[16] The "natural" collateral vessels have a very thin muscular coat as well as a small caliber and the increase in the smooth muscle component of these vessels is probably an important aspect of acquired responsiveness to nitroglycerin. It remains to be determined whether collateral tortuosity as a morphologic marker readily identifiable at the time of coronary angiography correlates with the ability of collateral vessels to respond to vasodilators.

Diameter and tortuosity of collateral vessel as an angiographic index of age of coronary occlusion: In our postmortem angiographic study it appears that the age of the coronary occlusion associated with infarction can roughly be estimated when vessels of determined diameter and tortuosity are fitted to the graph

in Figure 4. The greater the collateral tortuosity, the older the age of infarction. Angiographic visualization of intercoronary collateral circulation has been used as an indirect sign of significant coronary arterial luminal narrowing, even if the coronary lesion is not readily apparent.[17] Our findings suggest that, in a similar fashion, the diameter and tortuosity of the collateral vessel may be a rough but useful angiographic index of age of vascular occlusion.

Clinical implications of a collateral tortuosity index: The importance of collateral vessels to the preservation of myocardium in patients with occlusive atherosclerotic disease is still uncertain and the subject of some controversy.[1] Although collateral vessels may take time to develop and acquire dimensions of value in human beings, and thus are of limited use in the setting of acute infarction, it is difficult to deny at least a potential value of a well developed collateral system to the long-term survivor of acute coronary occlusion. Whether the course of survivors of acute myocardial infarction in terms of reinfarction, late arrhythmias or sudden death is influenced by the degree of collateral proliferation or its time course of development are important issues to resolve, especially if interventions become available that can selectively enhance such collateral growth. A tortuosity index may be of use in such determinations.

In conclusion, the growth of collateral vessels, like the growth of normal vessels, is by both dilatation and lengthening. Increased length is appropriate for the growing body but in the collateral vessel, which is constrained by relatively fixed points of origin and termination, the excess length is accommodated by increasing tortuosity. The extent to which a collateral channel of a given size is tortuous is an indication of the time it has functioned as a bypass for an obstructed vessel.

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Angiographic Evaluation of the Natural History of Normal Coronary Arteries and Mild Coronary Atherosclerosis

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Between September 1966 and September 1976, a group of 48 patients with normal coronary arteries or nonsignificant coronary atherosclerosis documented in a first coronary arteriogram underwent a second angiogram because of persistent or recurrent chest pain. The interval between studies was 13 to 108 months (mean 42 months). The indication for the first angiogram was typical or atypical anginal pain. The patients were separated into two groups according to the results of the first angiogram. Group I included 22 patients, 9 men and 13 women, with normal coronary arteries (mean age 49 years, range 28 to 62). Group II included 26 patients, 18 men and 8 women, with coronary stenosis of less than 50 percent of intraluminal diameter (mean age 49 years, range 38 to 63). The second angiogram revealed normal coronary arteries in all 22 patients in Group I but showed progression of disease in 7 (27 percent) of the 26 patients in group II. The coronary arterial narrowings were greater than 50 percent in four patients and greater than 70 percent in only two patients. The clinical course, coronary risk factors and interval between angiograms were not useful predictors of progression of disease. The data suggest that coronary artery disease is unlikely to develop in adults with normal coronary arteries and that roughly 75 percent of adults with nonsignificant atherosclerosis will not show progression of disease over a 3 to 4 year period.

Previous reports[1,2] have shown that at least one third of patients undergoing coronary arteriography for the evaluation of chest pain have normal coronary arteries or mild nonobstructive atherosclerosis. Whereas the natural history of patients with obstructive coronary disease has been widely reported,[3–5] little has been written about the course of patients with normal coronary arteries or nonsignificant atherosclerosis. Their clinical prognosis is generally believed to be benign[6,7] although many remain symptomatic years after their initial coronary arteriogram.[6] It is often not clear whether the persistence of symptoms is related to the development or the progression of coronary disease. Knowledge of the rate of progression of coronary atherosclerosis is important both for the long-term management of this large group of patients and for better insight into the natural history of coronary disease in general. Therefore, in this study we evaluated angiographic developments in patients with normal coronary arteries or minimal nonobstructive coronary disease.

Material and Methods

Between September 1966 and September 1976, a total of 8,630 patients had coronary arteriograms at the Montreal Heart Institute. Of these, 2,025 (23 percent) had normal coronary arteries and 838 (10 percent) had nonobstructive coronary disease (less than 50 percent stenosis of intraluminal diameter). Among these, 48 patients were studied who met the following criteria: (1) two examinations performed at intervals of more than 12 months; and (2) coronary arteriograms of good technical quality to allow adequate comparison between studies.

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TABLE I

Patient Material

	Group I*	Group II*
Patients (no.)	22	26
Associated cardiac disease (no. of patients)	13	8
Men (no. and percent)	9 (41%)	18 (70%)
Age (yr) (average and range)	49 (28–62)	49 (38–63)
Interval between studies (mo) (average and range)	52 (13–108)	37 (14–86)

* Group I = normal coronary arteries; Group II = coronary stenosis of less than 50 percent.

Patients with associated cardiac lesions who required sequential studies were not excluded.

The average interval between examinations was 42 (13 to 108) months. The first coronary arteriogram was usually obtained to evaluate typical or atypical chest pain. The second angiogram was later required because of persistent or recurrent anginal pain or because of the development of a significant cardiac event.

Patients: The patients were separated into two groups according to the results of the first coronary arteriogram (Table I). Group I consisted of 22 patients with normal coronary arteries. There were 9 men and 13 women with a mean age of 49 (28 to 62) years. Group II contained 26 patients with less than 50 percent coronary stenosis. There were 18 men and 8 women with a mean age of 49 (38 to 63) years. The time interval between studies was approximately 4 1/2 years in group I and 3 years in group II. Thirteen patients in group I and eight patients in group II had associated cardiac lesions such as cardiac valve disease or cardiomyopathy. In addition, two patients in group I had mitral valve prolapse and one had Prinzmetal's angina. Two patients each in groups I and II had an intercurrent myocardial infarction.

Patients in group II were then classified into two subgroups according to whether the coronary lesions evident in the second angiogram remained unchanged (group IIa: nonprogressive atherosclerosis, 19 patients) or increased (group IIb: progressive atherosclerosis, 7 patients).

Clinical data: In all patients, clinical data between studies and atherosclerotic risk factors were recorded. Typical angina was noted when pain of constrictive or oppressive character, localized in the precordium, was precipitated by exertion and relieved by rest. Atypical pain consisted of thoracic pain or discomfort that was in part characteristic of typical angina.

TABLE II

Coronary Anatomy in Group II (coronary stenosis of less than 50 percent)

	Cases (no.)
Degree of stenosis	
≤25%	11
<50%	15
Site of lesion	
Left anterior descending coronary artery	20
Left circumflex coronary artery	12
Right coronary artery	17
Number of arteries diseased	
One	9
Two or three	17

A family history of coronary artery disease was noted when angina or a coronary event occurred before age 50 in one or more first degree relatives. Smoking was defined as the use of at least 10 cigarettes a day for at least 5 years. High blood pressure was considered present when the diastolic blood pressure was greater than 100 mm Hg on three successive occasions. Blood lipid abnormalities were defined as a serum cholesterol level greater than 250 mg/100 ml or serum triglyceride values greater than 180 mg/100 ml, or both. Diabetes was defined as a persistent elevation of blood glucose level requiring administration of either insulin or orally given hypoglycemic agents.

Coronary arteriography: The technique used at this institution has previously been described.[8] The angiographic films were interpreted successively by an experienced cardiovascular radiologist. Angiographic progression of disease was recorded when there was a new stenosis of 25 percent or more of the intraluminal diameter of the artery or if a preexisting stenosis increased to 25 percent or more.

Results

Normal Coronary Arteries

Coronary atherosclerosis did not develop in any of the 22 patients in group I even though 2 patients had a well documented myocardial infarction. The interval between examinations averaged 4 1/2 years in the total group and exceeded 4 years in 11 patients.

Less than 50 Percent Coronary Stenosis

Initial angiograms: Table II shows the distribution and severity of lesions in patients in group II. Eleven had stenosis equal to or less than 25 percent and 15 had stenosis of more than 25 percent but less than 50 percent. The left anterior descending coronary artery was the most commonly diseased artery. Nine patients had plaques limited to a single coronary artery and 17 had plaques in more than one artery.

Follow-up angiograms: Seven of the 26 patients (27 percent) in group II had progression of disease after an average interval of 3 years. Atherosclerosis progressed in 12 arteries of the seven patients (Table III). Five of the 12 arteries manifested progression to more than 50 percent stenosis and two showed progression to complete occlusion (Fig. 1).

Table IV lists the arteriographic findings in the patients who had progression of disease at the time of their second arteriogram, which was performed an average of 46 months after the first (group IIb). Of five patients restudied for persistent atypical angina three had progression to stenosis of less than 50 percent of the in-

TABLE III

Results of the Second Coronary Arteriogram

	Progression of Disease	
	Patients (no.; %)	Arteries (no.)
Group I*	0 of 22	0
Group II*	7 of 26 (27%)	12

* Group I = normal coronary arteries; Group II = coronary stenosis of less than 50 percent.

TABLE IV

Coronary Arteriographic Findings in Seven Patients in Group IIb (progressive atherosclerosis)

Case no.	Interval Between Studies (mo)	Progression of Disease		
		LAD	LCx	RCA
		Symptoms Unchanged		
1	14	M → 25%	N	N → 25%
2*	60	M → 30%	N → 25%	N
3	40	M → 40%	10 → 35%	N → 40%
4	25	30 → 60%	N → 60%	M → 30%
5	77	30 → 60%	M → 25%	30 → 100%
		Atypical Angina → Typical Angina		
6	20	N	20 → 60%	30%
7	86	N → 100%	N → 100%	25 → 95%

* Idiopathic hypertrophic subaortic stenosis.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = minimal disease; N = no disease; RCA = right coronary artery; → = degree of progression of disease.

traluminal diameter and two manifested stenosis of more than 50 percent. Significant obstructive disease developed in the two patients with atypical angina who later manifested typical angina. Stenosis of 70 percent or more of the intraluminal diameter developed in only two patients.

Of the two patients in group II with documented myocardial infarction before the repeat coronary angiograms, one showed no progression of disease and the second (Case 7) had the most extensive progression of disease in the study.

Role of coronary risk factors: The presence of coronary atherosclerosis in group II patients was more common in men than in women (difference not significant) and in smokers ($P < 0.01$). No other risk factor allowed discrimination between the presence or absence of coronary disease. Progression of disease was more frequent in patients younger than 45 years ($P < 0.025$). None of the coronary risk factors assessed allowed us

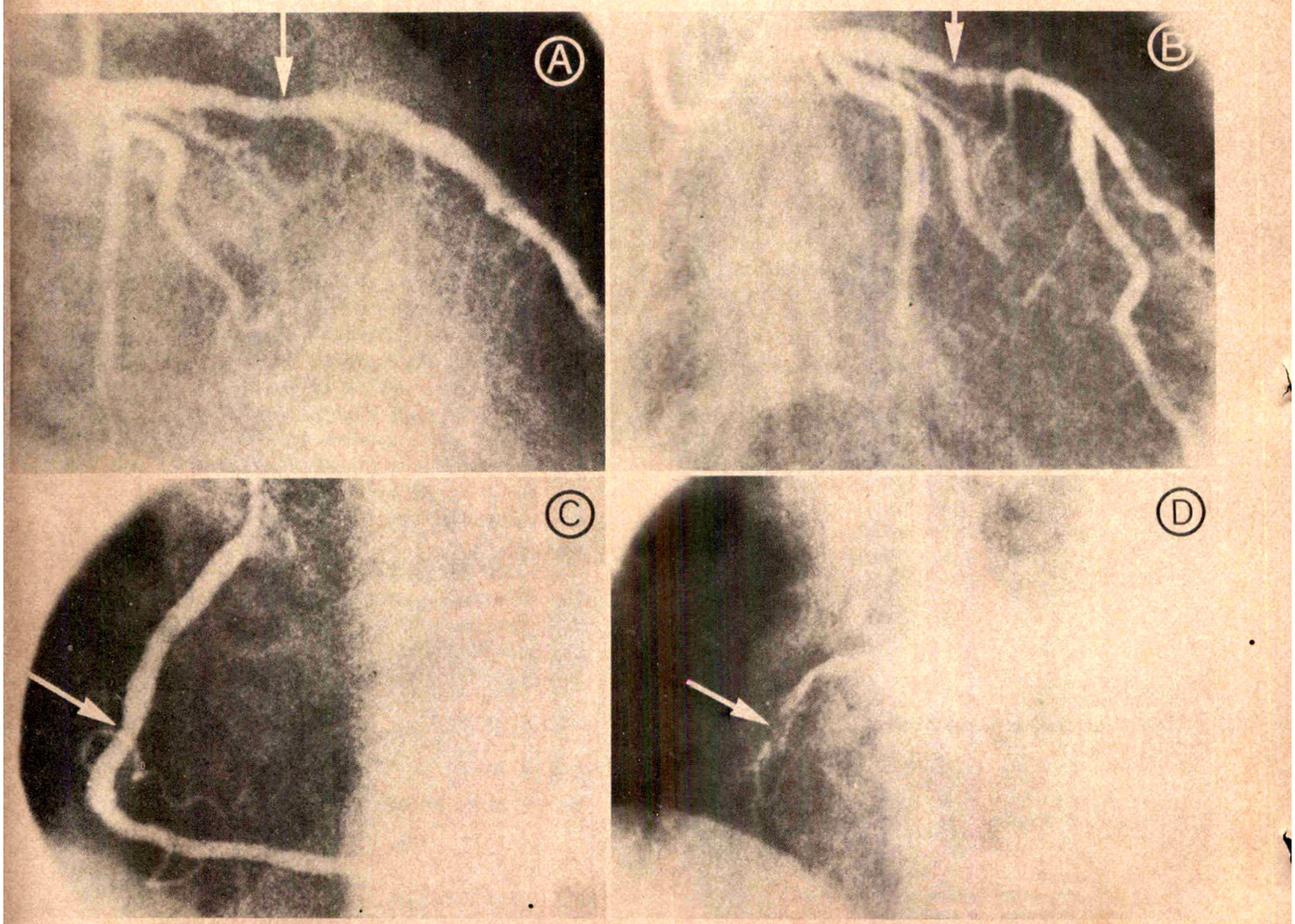

FIGURE 1. Case 5 (Table IV). The coronary angiogram shows progression of disease 6 years after the initial arteriogram. A 30 percent stenosis in the left anterior descending coronary artery (**A**) has progressed to 60 percent (**B**); a 25 percent stenosis in the left circumflex artery (not seen in this projection) remains unchanged. A 30 percent stenosis in the right coronary artery (**C**) has progressed to complete obstruction (**D**).

TABLE V

Risk Factors in Groups I and II*

	Group I	Group II		
		Total	IIa	IIb
Cases (no.)	22	26	19	7
Male subjects (no. and percent)	9 (41%)	18 (70%)	12 (63%)	6 (86%)
Mean age (yr)	49	47	47	45
Risk factors (no. and percent)				
<45 years old	8 (36%)	8 (31%)	3 (16%)	5 (71%)‡
Hyperlipidemia	12 (55%)	14 (54%)	9 (47%)	5 (71%)
Smoking	7 (32%)	20 (77%)†	14 (73%)	6 (86%)
Hypertension	2 (9%)	2 (8%)	2 (11%)	1 (14%)
Family history of CAD	2 (9%)	3 (12%)	2 (11%)	1 (14%)
Diabetes mellitus	0	1 (4%)	1 (5%)	0

* Group I = patients with normal coronary arteries; Group II = patients with coronary stenosis <50 percent; Group IIa = group II patients with no interval progression of disease; Group IIb = group II patients with interval progression of disease. CAD = coronary artery disease.
† $P < 0.01$.
‡ $P < 0.025$.

to predict which patients were more susceptible to progression of coronary disease (Table V).

Discussion

Obstructive coronary disease: The natural history of obstructive coronary disease has been widely reported.[4,5,9–13] Sequential coronary arteriograms in patients with severe obstructive coronary disease have shown that progression of disease can be frequent, rapid and highly unpredictable.[9–13] It was observed to occur within 1 to 2 years in 52 to 76 percent of patients studied for a change in symptoms. Rösch et al.[13] reported that after an average interval of 26 months, 33 percent of coronary obstructions were worse and disease progressed in an average of two arterial sites per patient. Subsequent progression was independent of overall severity of initial disease or prior disease at the site of progression and occurred frequently in previously normal vessels.[9] Data on the influence of clinical symptoms and coronary risk factors on progression of disease have been variable.

It has been shown that the clinical course and prognosis of coronary disease are related more to the severity of coronary atherosclerosis assessed angiographically than to any other factor.[3–5] Impaired ventricular function independently affects yearly mortality.

Normal coronary arteries: For obvious reasons, much less is known of the angiographic follow-up and prognosis of patients with normal coronary arteries or minimal nonsignificant coronary atherosclerosis. Gensini et al.[12] reported that 44 of 46 patients with normal coronary arteries did not manifest evidence of coronary disease an average of 52 months after the initial arteriogram although their average age was nearly 50 years. The exceptions were two diabetic men with hypertension. In both patients, a single vessel was involved and the lesion was less than 75 percent. Kimbiris et al.[11] reviewed data on 12 patients with normal coronary arteries. After an interval of 33 months, the second radiologic examination reaffirmed the presence of normal coronary arteries in all patients. Rösch et al.[13] reported on 11 patients with valve disease and normal coronary arteries. Follow-up angiography showed normal findings in nine patients after a mean interval between studies of 39 months. In two patients, four stenoses were found on follow-up studies performed at intervals of 32 and 55 months, respectively. These stenoses were of minor degree (less than 50 percent). Finally, Bruschke et al.[14] described serial angiograms in six patients with normal coronary arteries who were restudied because of persistent symptoms. After an interval of 10 to 84 months, two patients manifested new stenosis: one had a lesion of less than 30 percent and the other had occlusion of the left anterior descending coronary artery 25 months after the initial study.

Our results demonstrate no development of coronary disease in 22 patients with normal coronary arteries after a minimal interval of 13 months and an average interval of 52 months. The combined data from these studies suggest that middle-aged adult men and women with normal coronary arteries rarely manifest subsequent coronary atherosclerosis.

It is generally believed that coronary disease begins at a relatively early age in the presence of a genetic predisposition and of factors that favor its development.[15,16] It has been suggested that the atherosclerotic process begins histologically during the first months of life.[17] Thickenings of internal vascular layers of the coronary vessels observed during childhood in some populations can be related to subsequent development of coronary atherosclerosis.[18] The nondevelopment of coronary atherosclerosis by the fourth and fifth decades of life warrants against its future presentation. However, one cannot rule out the possibility that the rare patient with later narrowing already had mild intimal changes not detected in the first coronary arteriogram.

Nonobstructive coronary disease: There are few data on the angiographic evolution of mild nonobstructive coronary atherosclerosis. Bruschke et al.[14] reported that patients with this condition have an excellent 5 year prognosis. The incidence rate of presumed cardiac death after 5 years of follow-up was 2 percent in 101 patients with stenosis of less than 30 percent, a

rate lower than that observed for an average population matched for age and sex. The incidence rate of presumed cardiac death in 57 patients with an intraluminal narrowing of more than 30 but less than 50 percent was 5.3 percent after 5 years, slightly more than that observed in the average population. In 14 patients with minimal lesions (less than 50 percent stenosis) who had serial angiograms because of persistent symptoms, 9 showed progression of disease after an average interval of 4 years; 7 patients manifested stenoses of more than 50 percent.

In our series of 26 patients with minimal lesions, 27 percent showed progression of coronary disease on restudy after an average interval of 3 years. However, only four patients (15 percent) had significant coronary disease (greater than 50 percent stenosis) and only two (8 percent) had stenosis of more than 70 percent. This small incidence of progression in a population restudied for worsening or persistent symptoms explains the excellent prognosis of these patients. This low rate of progression in middle-aged adults compared with that in patients with significant obstructive coronary lesions is probably related to the pathophysiology of coronary disease. The process tends to begin early in life and to evolve in episodes, at times not showing a progressive character.[19]

The duration, character and evolution of symptoms were not helpful in separating patients with and without coronary atherosclerosis or those whose atherosclerosis showed signs of progression.[9]

Implications: Our study, like most retrospective studies, dealt with a selected group of symptomatic patients. Thus, our conclusions may not be applicable to unselected asymptomatic men and women. Sequential coronary arteriograms from childhood to middle age in asymptomatic persons would clarify the timing of development of coronary disease, but these studies cannot now be justified.

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Incidence and Significance of Decreases in Systolic Blood Pressure During Graded Treadmill Exercise Testing

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The incidence of decreases in peak systolic blood pressure during treadmill exercise was investigated in 460 patients with definite or suspected coronary heart disease. All patients were studied with coronary cineangiography. Exercise was continued to one of the following end points: chest pain, 85 to 90 percent of the patient's age-predicted maximal heart rate, ventricular tachycardia or a sustained decrease of 10 mm Hg or more below the peak level of systolic blood pressure. Twenty-two patients with 75 percent or greater stenosis of one or more major coronary arteries manifested a decrease in systolic pressure 10 mm Hg or more during exercise. These included 15 (17 percent) of 88 patients with three vessel, 7 (7 percent) of 101 with two vessel and 0 of 90 with single vessel disease. The decrease in pressure was reproducible in the seven patients who underwent a second exercise test before alteration of therapy; this decrease was abolished in the six patients who exercised again after coronary bypass graft surgery.

A decrease in systolic pressure of 10 mm Hg or more also occurred during exercise testing in 3 of 23 patients with noncoronary organic heart disease; all 3 had an obstructive cardiomyopathy that had not been suspected clinically. Only 1 of 158 subjects with chest pain and no demonstrable heart disease had a decrease in systolic blood pressure with exercise. Declines in blood pressure were not observed during 650 maximal exercise tests performed on 560 clinically normal men.

In conclusion, if one excludes subjects with cardiomyopathy or significant heart valve disease, a sustained exercise-induced decrease in peak systolic blood pressure of 10 mm Hg or more is a highly specific sign of multiple vessel coronary artery disease. This phenomenon is best explained by acute left ventricular pump failure secondary to extensive myocardial ischemia.

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In normal subjects exercise produces an increase in systolic blood pressure, and this increase is usually accompanied by a decrease in the diastolic blood pressure with a widening of the pulse pressure.[1,2] A decrease in systolic blood pressure below resting levels has been observed during treadmill exercise testing in some patients with severe valve, hypertensive or coronary heart disease[3]; a decrease in systolic pressure below resting levels at the onset of treadmill exercise-induced angina has been reported as a reliable sign of severe multiple vessel coronary artery disease.[4] However, Baker et al.[5] reported that a decreasing systolic blood pressure may be observed during graded exercise in the absence of significant coronary artery disease, especially in women. Other study results[6,7] have suggested that a reduction in systolic pressure may be a normal physiologic response during prolonged strenuous exercise. Thus, there are conflicting reports regarding the significance of decreasing systolic blood pressure during graded exercise testing. Furthermore, it is not known how great a decrease in systolic blood pressure is necessary

to be of potential diagnostic aid when evaluating patients with suspected coronary artery disease.

This report deals with the findings of a prospectively designed study of the blood pressure responses during treadmill exercise testing of 460 patients with known or suspected coronary heart disease. During the time of this study we also evaluated the blood pressure responses of 560 normal male members of the Indiana State Police Force who underwent a total of 650 maximal treadmill exercise tests.

Material and Methods

Cases: A total of 1,020 persons from two patient populations were evaluated by treadmill exercise testing. Group I consisted of 560 clinically healthy male members of the Indiana State Police Force who underwent periodic maximal exercise testing during the study period as part of a continuing cardiovascular evaluation program being conducted at the Indiana University Medical Center.[8] Group II consisted of 460 consecutive patients who underwent both treadmill exercise testing and coronary cineangiographic studies at our institution between July 1, 1973 and September 30, 1976 because of known or suspected coronary artery disease. Our modified Balke multistage exercise protocol and our electrocardiographic recording techniques have previously been described.[8,9]

Blood pressure recordings: All exercise blood pressure levels were measured by the same observer during each individual exercise test. However, three of us participated in the supervision of the exercise tests reported in this study, and serial testing of the same patient was occasionally performed by a different physician. The blood pressure recordings were made with a Tycos cuff adapted to a Baumanometer sphygmomanometer and a standard stethoscope with the diaphragm placed over the right brachial artery. Blood pressures were recorded in the subjects in Group I during sitting and standing rest and during the last minute of each 3 minute stage of exercise. Blood pressures in the patients in Group II were recorded at least once per minute during each 3 minute stage of exercise. During exercise all blood pressure recordings were made with the subject's hand resting on a side rail and his arm flexed slightly at the elbow. This technique reduces the amount of mechanical or arm movement artifacts and assures accurate and reproducible blood pressure measurements. Whenever a decrease was observed in the systolic pressure, the blood pressure recordings were repeated one or more times at approximately 15 second intervals to confirm the accuracy of the reading and to demonstrate that the decrease was sustained. By study protocol design, a decrease in systolic blood pressure of 10 mm Hg or more that was sustained during two or more consecutive determinations was considered an end point for the exercise test.

Coronary cineangiographic studies: In the patients in Group II these studies were performed utilizing the Judkins transfemoral approach.[10] Each coronary artery was filmed in multiple projections using 35 mm cineangiography. All coronary cineangiograms were reviewed and interpreted by three of us, and arteries unanimously graded as having a 75 percent or greater luminal narrowing were considered significantly narrowed. The presence and extent of left ventricular wall motion abnormalities were estimated using a left ventriculogram filmed in the right anterior oblique position. Left ventricular end-diastolic pressure was measured in the resting state before the left ventricular and coronary cineangiographic injections.

Exercise protocol: *The subjects in Group I* underwent a thorough history, physical and laboratory examination before exercise testing.[8] All men with definite or suspected heart disease were excluded from this study. Also excluded were subjects with persistent systolic blood pressure at rest exceeding 160 mm Hg or diastolic pressure exceeding 96 mm Hg. The end point of exercise for these highly motivated subjects was a self-determined maximal effort; all subjects attained an exercise heart rate exceeding 90 percent of their age-predicted maximal rate.[11]

The exercise end points for the patients in Group II were one of the following: (1) chest pain, (2) an exercise heart rate of 85 to 90 percent of the patient's age-predicted maximal rate, (3) ventricular tachycardia, or (4) a decrease in systolic blood pressure of 10 mm Hg or more sustained during repeat blood pressure determinations. In patients who experienced chest pain during exercise, the test was terminated shortly after the onset of pain if a diagnosis of coronary heart disease was already established or if the S-T segment response was interpreted as abnormal by the monitoring physician (1.0 mm or more of horizontal or downsloping S-T depression). If the S-T segment response remained normal or equivocal at the time of exercise-induced chest pain and a diagnosis of coronary heart disease was not established, the test was sometimes continued in an effort to elicit an abnormal S-T segment re-

TABLE I

Prevalence of Exercise-Induced Decreases in Systolic Blood Pressure (EDBP) in the Study Populations

	Subjects	Exercised (no.)	Sex (no.)	Mean Age (Range) (yr)	With EDBP no.	With EDBP %
Group I	Clinically normal state police	560	M-560 F-0	38(28–61)	0	0
Group IIA	Chest pain—no significant coronary artery disease*	159	M-89 F-70	47(26–68) 50(17–68)	1† 0	0.6
Group IIB	Significant coronary artery disease‡	279	M-242 F-37	51(18–69) 54(35–69)	22 0	7.9
Group IIC	Noncoronary heart disease§	22	M-17 F-5	43(30–61) 47(43–50)	3 0	13.6

* No coronary stenosis greater than 50 percent. There were no obstructive lesions in 145 (91 percent) of the 159 subjects.
† The only patient in the study who was receiving methyldopa and propranolol at the time of exercise testing.
‡ One or more major coronary arteries with 75 percent or greater stenosis.
§ Includes 19 patients with cardiomyopathy. The three patients with exercise-induced decreases in systolic blood pressure were the only ones in this study group with obstructive cardiomyopathy.

sponse. However, the patient's chest pain was never allowed to exceed the intensity of that he experienced during his usual daily activities.

All exercise electrocardiograms were recorded on magnetic tape. Upon completion of the exercise test the S-T segment changes were quantitated using previously described computer techniques.[9] In patients with a normal baseline ST-T segment, the computed S-T response was considered abnormal if the S-T depression was 1.0 mm or greater and the algebraic sum of the S-T depression in millimeters and the S-T slope in millivolts/second was less than zero.[9] These computed values were used to compare the incidence of abnormal S-T segment responses in patients with and without exercise-induced declines in systolic blood pressure.

Results

Group I (normal subjects): The 560 clinically normal subjects in Group I underwent a total of 650 maximal exercise tests during the study period. None of these subjects demonstrated a decrease in systolic blood pressure during exercise (Table I).

Group II (known or suspected coronary artery disease): The patients in this group were divided into three subgroups according to their final clinical diagnosis (Table I). Group IIA consisted of 159 patients who were evaluated for symptoms of chest pain but found to have no coronary artery stenosis exceeding a 50 percent luminal narrowing by coronary cineangiography; the majority (91 percent) demonstrated no coronary artery disease or only minor luminal irregularities. In one patient, a 41 year old man with essential hypertension, systolic pressure decreased 24 mm Hg during exercise. He had no chest pain and at the time of the exercise test he was taking propranolol (40 mg four times a day), methyldopa (250 mg three times a day) and long-acting nitrates (Nitrobid®, 6.5 mg three times a day). Group IIB consisted of 279 patients who demonstrated a 75 percent or greater stenosis of one or more of the three major coronary arteries on coronary cineangiography. In this subgroup there were 22 patients (7.9 percent) who demonstrated a decrease in systolic blood pressure of 10 mm Hg or more during exercise. Group IIC consisted of 22 patients with noncoronary organic heart disease; 16 had nonobstructive cardiomyopathy, three had obstructive cardiomyopathy, two had aortic insufficiency and one had a partial absence of the pericardium. Three of these patients demonstrated a decrease in systolic blood pressure during exercise and all three had an obstructive cardiomyopathy.

Patients with exercise-induced decline in systolic blood pressure: A total of 39 exercise tests were performed in these 26 patients. All of the repeat exercise tests were performed in the 22 patients with coronary artery disease in Group IIB. The Group IIB patients demonstrated a mean decline in systolic blood pressure of 23 mm Hg during their initial exercise test (Table II). The systolic blood pressure level during exercise dropped below that recorded during standing rest in only 9 of the 22 patients. Sixteen of these 22 patients had angina before the decrease in blood pressure; the limiting symptoms in the remaining 6 were dyspnea in 3, leg fatigue in 2 and giddiness in 1.

A second exercise test was obtained in 7 of the 22 patients with coronary disease who demonstrated a decrease in systolic blood pressure during their initial test (Group IIB, Table II). The repeat tests were performed without intervening alterations in therapy and after time intervals ranging from 2 weeks to 17 months (the interval was 2 to 5 weeks in all but one patient). The decrease in systolic blood pressure during exercise was reproducible in all seven patients.

The most dramatic and abrupt decreases in systolic pressure were observed in the three patients with obstructive cardiomyopathy (Group IIC, Table II). These patients were being evaluated because of chest pain of uncertain origin and they did not have heart murmurs at rest or pathologic Q waves in the resting electrocardiogram. Prominent systolic murmurs were observed immediately after exercise, and a diagnosis of obstructive cardiomyopathy was subsequently confirmed with echocardiography and left heart catheterization.

Effect of surgery: Saphenous vein coronary bypass graft surgery was subsequently performed in 12 of the 22 patients with coronary artery disease (Group IIB). To date we have repeated the exercise test in 6 of the 12 patients postoperatively including 4 patients who demonstrated a decrease in systolic blood pressure during repeat exercise testing before surgery (Table II).

TABLE II

Magnitude and Reproducibility of Exercise-Induced Decrease in Systolic Blood Pressure (EDBP) in 26 Patients During 39 Exercise Tests

	Patients (no.)	With TMET (no.)	With EDBP (no.)	Mean and Range of EDBP (mm Hg)	With EDBP Below Standing BP at Rest (no.)
Group IIA	1	1	1	24	1
Group IIB	22				
First TMET	. . .	22	22	23 (10–46)	9
Repeat TMET	. . .	7	7	20 (10–34)	2
Repeat TMET after CABG	. . .	6*	0	. . .	. . .
Group IIC	3	3	3	39 (20–56)	2

* Four of these patients were in the subgroup of seven patients who had a second or repeat treadmill test. All four had a reproducible exercise-induced decrease in systolic blood pressure before surgery.

BP = blood pressure; CABG = coronary bypass graft surgery; TMET = treadmill exercise test.

All six of the patients demonstrated an increase in the peak systolic blood pressure attained during repeat exercise testing after surgery (Fig. 1). The mean increment in systolic pressure was 29 mm Hg (range 4 to 68). Two of the six patients still experienced angina during the postoperative exercise test, but every patient was able to exercise for a longer period than before surgery (mean duration 308 seconds preoperatively versus 638 seconds postoperatively).

Clinical characteristics of patients with a decrease in systolic blood pressure during exercise (Table III): The 22 patients with coronary artery disease and exercise-induced decreases in systolic blood pressure were, as a group, 4.4 years older than the 257 patients who did not have a decrease in systolic blood pressure during exercise. This age difference between the two subgroups was not statistically significant. All 22 patients were men (22 of 242). There were 37 women in the study group with significant coronary artery disease. The absence of a decrease in systolic blood pressure in women compared with men (0 of 37 versus 22 of 242) was not quite significant at the 0.05 level. This apparent sex difference was most likely due to a predominance of single vessel disease in the women and to a much greater prevalence of triple vessel disease in the men. No significant differences were observed between the two subgroups (those with and without a decrease in systolic blood pressure) in the frequency of computer-quantitated S-T segment abnormalities with exercise, the presence of ventricular premature complexes, the prevalence of previous myocardial infarction, evidence of akinesia or dyskinesia in the left ventriculogram or the level of mean left ventricular end-diastolic pressure (Table III).

The coronary arteriographic findings in the 22 patients with coronary artery disease and exercise-induced decreases in systolic blood pressure are summarized in Table IV. Three patients had significant stenosis of the left main coronary artery, and an additional 14 patients had a 75 percent or greater stenosis of the luminal diameter of both the left anterior descending and left circumflex coronary arteries. Therefore, 17 of the 22 patients had lesions that have been regarded by some investigators[4] as equivalent to a left main stem coronary artery stenosis. Fifteen (68 percent) of the patients had significant three vessel coronary disease. The remaining seven patients had at least two major coronary arteries with a 75 percent or greater stenosis and four of these patients also had a 50 percent stenosis of the third major coronary artery.

The prevalence rate of exercise-induced decreases in systolic blood pressure in the 279 patients with coronary

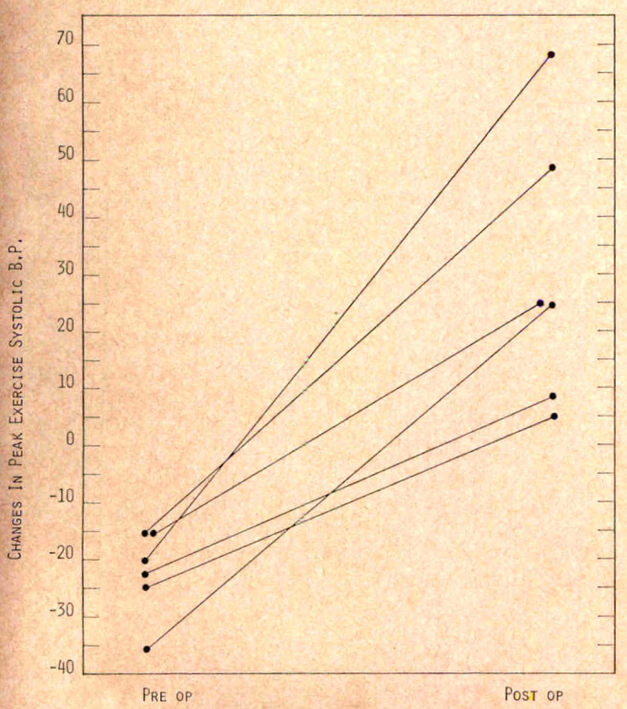

FIGURE 1. Effect of coronary bypass surgery in six patients. Preoperatively (PRE OP) these six patients had a mean decrease of 23 mm Hg from peak exercise systolic blood pressure level (B.P.). Postoperatively (POST OP) each patient attained a higher peak systolic blood pressure level than on the preoperative exercise test, with a mean increment of 29 mm Hg.

TABLE III

Characteristics of 279 Patients With Significant Coronary Artery Disease

	22 With EDBP	257 Without EDBP	*P* Value
Mean age (yr)	55.2	50.8	NS
Sex (no.)			
Male	22	220	
Female	0	37	NS
S-T depression with exercise testing*	88% (15/17)	78% (142/183)	NS
VPC	55% (12/22)	49% (126/257)	NS
Previous documented myocardial infarction	46% (10/22)	49% (125/357)	NS
Akinesia or dyskinesia on left ventriculography	32% (7/22)	39% (98/254)†	NS
Mean LVEDP (mm Hg)	11.7	11.2	NS

* Includes only patients with a normal baseline ST-T segment.
† A left ventriculogram was not obtained in three patients.
EDBP = exercise-induced decrease in systolic blood pressure; LVEDP = left ventricular end-diastolic blood pressure; NS = not significant; *P* = probability; VPC = ventricular premature complexes at rest or with treadmill exercise.

TABLE IV

Coronary Arteriographic Findings in 22 Patients (Group IIB)

	Patients (no.)
≥75% stenosis of:	
Left main coronary artery	3
Left anterior descending artery (LAD)	19
Left circumflex artery (LC)	18
Right coronary artery (RCA)	19
LAD and LC	17
LAD and RCA	16
2 major vessels	7
3 major vessels	15

artery disease was 7.9 percent, but this varied considerably within our study population depending on the number of coronary vessels involved (Table V). None of the 90 patients with single vessel disease manifested a decrease in systolic blood pressure during exercise whereas 7 percent (7 of 101) of the patients with two vessel disease and 17 percent (15 of 88) of those with three vessel disease demonstrated an abnormal systolic blood pressure response during exercise. Thus, a decrease in systolic blood pressure during exercise was observed in 11.6 percent (22 of 189) of patients with cineangiographic evidence of multiple vessel coronary artery disease. The prevalence rate of abnormal blood pressure responses in patients with left main coronary artery disease was 17 percent (3 of 18), which was the same as that observed in patients with significant three vessel disease. All three patients with significant left main coronary artery stenosis and an abnormal blood pressure response during exercise also had a 75 percent or greater stenosis of the right coronary artery.

TABLE V

Correlation of Severity of Coronary Artery Disease and Frequency of Exercise-Induced Decrease in Systolic Blood Pressure (EDBP) in 279 Patients

	Patients (no.)	With EDBP	
		no.	%
Single vessel with ≥75% stenosis	90	0	0
Two vessels with ≥75% stenosis	101	7	7
Three vessels with ≥75% stenosis	88	15	17

Discussion

Incidence and clinical significance of exercise-induced drop in systolic blood pressure: Our results reaffirm the clinical value of accurate blood pressure recordings during graded exercise testing. Previous reports[3,4] dealing with the exercise blood pressure responses of patients with heart disease have considered flat systolic blood pressure responses or a reduction in systolic blood pressure below resting levels to be abnormal. Our results show that a sustained and reproducible decrease in peak systolic blood pressure during exercise as small as 10 mm Hg is clinically significant. This observation holds true even when the initial expected increment in systolic blood pressure occurs during exercise. In patients with coronary artery disease a decrease of this magnitude in systolic blood pressure is highly suggestive of significant multiple vessel involvement. In our study population, 11.6 percent (22 of 189) of the patients with coronary cinenagiographic findings of advanced two or three vessel coronary artery disease demonstrated an abnormal decrease in blood pressure during exercise. Of the 88 patients who had triple vessel disease, 15 (17 percent) had an abnormal blood pressure response. Abnormal decreases in systolic blood pressure were not observed in healthy subjects or in patients with single vessel coronary artery disease.

The 22 study patients with exercise-induced decreases in systolic blood pressure were all identified on exercise tests performed before coronary cineangiography, and therefore there was no retrospective influence on their selection. None of the patients had orthostatic hypotension, hypovolemia, obstructive heart valve disease or evidence of congestive heart failure, and none had cardiac arrhythmia at the time of the exercise blood pressure determinations. Although one can question the accuracy of brachial arterial cuff pressure measurements taken during exercise, the reproducibility of an exercise-induced decrease in systolic blood pressure in all seven subjects undergoing a second exercise test and the absence of this finding in 560 normal men during maximal treadmill testing confirms that the blood pressure can be recorded during exercise with a high degree of reliability.

Causes of exercise-induced fall in systolic blood pressure: The decrease in the peak systolic blood pressure during exercise in patients with multiple vessel coronary artery disease is best explained by acute left ventricular pump failure secondary to extensive myocardial ischemia. This hypothesis is supported by an absence of abnormal blood pressure responses in our 90 patients with single vessel coronary disease, in whom less myocardium is at risk of ischemic compromise, and by the restoration of a normal blood pressure response to exercise in patients with multiple vessel disease after coronary artery bypass graft surgery. Because a decline in systolic blood pressure during exercise is primarily dependent upon the area of myocardium rendered ischemic, it is possible that some subjects with single vessel coronary artery disease will eventually be shown to manifest this abnormality. This could especially be the case when a maximal exercise protocol is used because the area of exercise-induced ischemia may be more extensive under these circumstances.

The abnormal blood pressure responses observed in the three patients with obstructive cardiomyopathy can best be attributed to an accentuation of the left ventricular outflow tract obstruction during treadmill testing. This is most likely due to a combination of an upright posture and the increase in circulating catecholamines that accompanies exercise.[12]

The explanation for the single patient with a "false positive" decrease in blood pressure among the 159 patients with chest discomfort and normal coronary arteriograms is less obvious. This patient was the only person in the study who was tested while receiving a combination of propranolol, methyldopa and long-acting nitrates. This drug combination has the potential for reducing maximal cardiac output while simultaneously augmenting the peripheral vasodilatation that accompanies exercise.[13–15] Therefore, certain pharmacologic agents may obliterate the adaptive mechanisms normally operative during exercise to maintain the systolic blood pressure.

Role of thermoregulatory mechanisms: Prolonged exhaustive exercise has been shown to cause a decrease in systolic blood pressure even in normal subjects.[6,7] This response is thought to be mediated through sympathetic vasodilatation of skin vasculature in order to

dissipate the heat load generated by the prolonged muscular work. As a larger percentage of the cardiac output is shifted to the skin for cooling purposes, the total peripheral vascular resistance decreases. If cardiac output is already near maximal, both the systolic and mean arterial blood pressures may decrease. This thermoregulatory or so-called "cardiovascular drift" phase of exercise[7] occurs only with vigorous exertion maintained over a prolonged period. This phenomenon was not observed by Saltin and Sternberg[6] using an exercise protocol including 15 minutes of warm-up followed by a maximal work load that would exhaust the subjects in another 6 minutes. With our modified Balke treadmill exercise protocol[8] none of the patients with an exercise-induced decline in systolic blood pressure walked more than 12 minutes (mean 4.9 minutes, range 2 to 12 minutes). Thus it is highly unlikely that the decrease in systolic pressure observed in the 22 patients was initiated by thermoregulatory mechanisms.

Our patient population was predominantly male but we did not observe an abnormal blood pressure response in any of the 37 women with coronary artery disease or in any of the 70 women who had chest pain but who were free of significant coronary artery disease on coronary cineangiography. Thus our results failed to confirm the finding of Baker et al.,[5] who reported that exercise-induced hypotension occurs more frequently in women and is often not associated with coronary artery disease.

Clinical implications: Our results show that a decrease in systolic blood pressure of 10 mm Hg or more below peak values during treadmill exercise is a reliable indicator of multiple vessel coronary artery disease provided the following conditions are met: (1) the decrease in pressure is sustained during one or more repeat determinations obtained at 15 to 20 second intervals after the initial recording; (2) there is no coexistent cardiomyopathy, heart valve disease, hypovolemia, orthostatic hypotension or evidence of congestive heart failure at rest; (3) there are no cardiac arrhythmias at the time of blood pressure recording; (4) the patient is not receiving a combination of pharmacologic agents that would significantly reduce cardiac output or augment the vasodilatation accompanying exercise, or both; and (5) exercise is at least 1 minute in duration. This latter condition is designed to exclude "false positive" decreases in systolic pressure in very anxious subjects whose pressure may decrease early in the first stage of exercise as they begin to relax. It is not necessary for the final systolic blood pressure to drop below that recorded at standing rest. Also, some subjects had normal exercise S-T segments (two patients) or did not experience angina (six patients). Therefore, when the criteria listed are fulfilled, we believe that an exercise-induced decrease of 10 mm Hg or more below peak systolic blood pressure is a useful, highly specific and easily elicited sign of severe compromise of the coronary circulation.

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Significance of Chest Pain During Treadmill Exercise: Correlation With Coronary Events

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A follow-up study of 1,402 patients with a positive maximal treadmill stress test was made to evaluate the significance of angina during the test. Life tables were constructed and evaluated for significance of age, sex and work load at onset of angina. Coronary events (myocardial infarction, progression of angina and coronary death) were twice as frequent in subjects with angina and S-T segment depression as in those without angina. The increased incidence in 4 years held for all coronary events and was still doubled at 7 years for progression of angina and coronary death. The incidence of coronary events was more than twice as great when the angina was induced by a light work load (4 metabolic equivalents = METS) as when it was induced by a heavy work load (8 to 9 METS). Men aged 41 to 50 years having angina during exercise testing had a 3-fold greater incidence of coronary events and a 4-fold greater incidence of myocardial infarction compared with their counterparts who had S-T segment depression alone.

In this study, angina during exercise testing identified 85 percent of true positive tests for coronary artery disease, whereas S-T depression alone identified only 64 percent of such tests. Thus, angina during exercise testing increases the sensitivity of the test and identifies cohorts of subjects at high risk for subsequent coronary events.

A number of variables in stress testing have previously been assessed in an attempt to identify patients with significant coronary artery disease.[1] The significance of angina during stress testing has not previously been elucidated. This study was designed to evaluate the presence of angina during maximal treadmill stress testing and its correlation with coronary events. The prognostic significance of stress testing was historically established by the follow-up study of Robb and Marks[2] on subjects given Master's two-step test reported in 1967 and supplemented for maximal treadmill testing by Ellestad and Wan in 1975.[1]

Material and Methods

Follow-up information, collected from referring doctors' records, was obtained on 1,402 patients who had a positive maximal treadmill stress test in this medical center between January 1, 1965 and July 1, 1976. A treadmill questionnaire was filled out by referring physicians or doctors' aides, and a trained research clerk reviewed the records for the following data: (1) presence, severity and progression of angina; (2) incidence and date of myocardial infarction; and (3) date and cause of death. All information was computerized and filed on disc in a CDC 3300 computer. The output provided the number of patients in each cohort, the number lost to follow-up, standard deviation of the mean and the cumulative percent of events at each interval. The vertical lines at each interval in the life tables indicate 2 standard deviations. When these limits do not overlap, the groups are significantly different ($P > 0.01$) by chi square analysis.

Protocol: Stress testing was performed according to the Memorial Hospital protocol.[3] The test was terminated if the patient reached the predictive maximal

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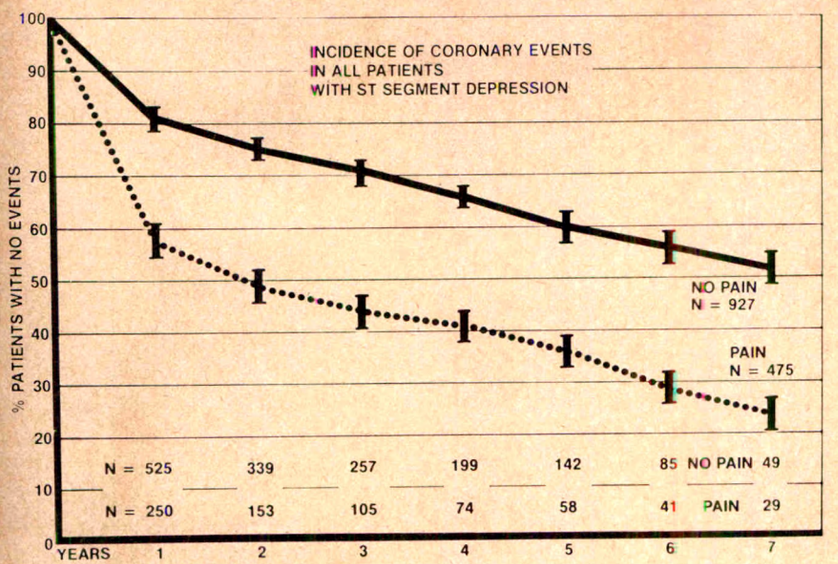


FIGURE 1. Life table illustrating the incidence of coronary events according to the presence or absence of chest pain during treadmill stress testing in all subjects with significant S-T segment depression. N = number of patients.

heart rate (as predicted by Åstrand et al),[4,5] or had worsening anginal pain (grade 3+), evidence of ischemia in the electrocardiogram, arrhythmias, progressively decreasing pulse or blood pressure or overwhelming fatigue. For the purpose of this study, the definition of chest pain was limited to symptoms reported by the patient and classified as characteristic of angina by the physician monitoring the test. During the test the patient was repeatedly questioned about the presence or absence of pain, its location, distribution and severity. He was asked to compare it with previous symptoms and was observed for clinical findings that might confirm or rule out the likelihood of coronary ischemia. The time course, site of pain and relation to breathing and position were especially noted.

Patients: The subjects had been referred for confirmation of suspected coronary artery disease, for quantitation of the degree of known coronary artery disease or for a routine screening test as part of an annual physical examination. Chest pain was the cause of referral of 72 percent of patients (67 percent of men and 93 percent of women). Surgically treated patients were excluded from the follow-up study.

Life tables were constructed according to the method of Cutler and Ederer.[6] The follow-up interval ranged from 6 months to 7 years.

Criteria for a positive test were at least 1.0 mm S-T segment horizontal or downsloping depression or 1.5 mm upsloping depression 0.08 second from the J point.

Results

The annual incidence of all coronary events over a 4 year period in these patients with a positive treadmill test was twice as great in patients who had S-T segment depression and chest pain during the test as in those who were free of angina during testing (Fig. 1 and 2). At

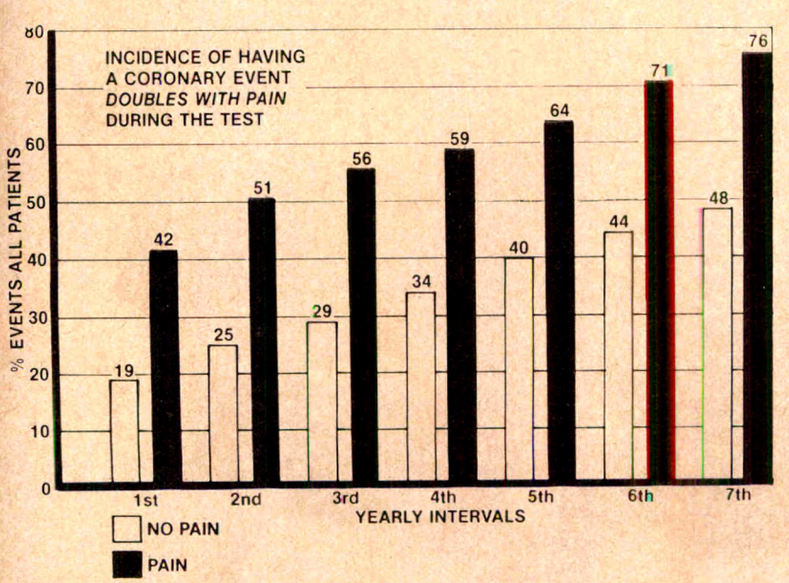


FIGURE 2. Bar graph demonstrating that the coronary events double at yearly intervals in all subjects with chest pain in addition to S-T segment depression during exercise testing.

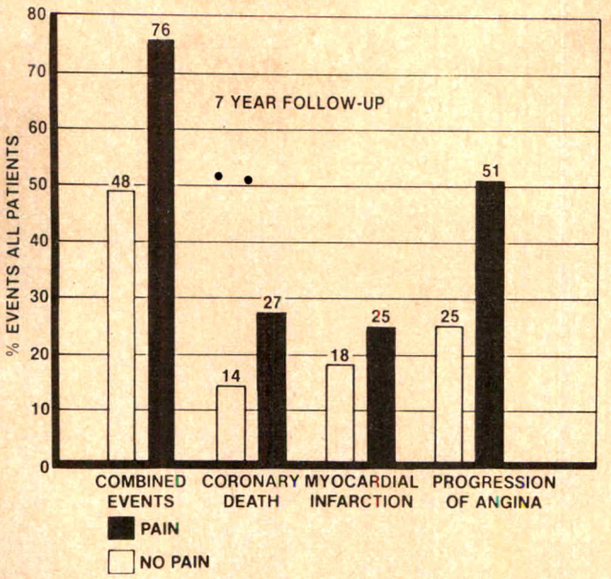


FIGURE 3. Bar graph at a 7 year follow-up period depicting the incidence of separate and combined coronary events according to the presence or absence of chest pain during exercise testing in all subjects.

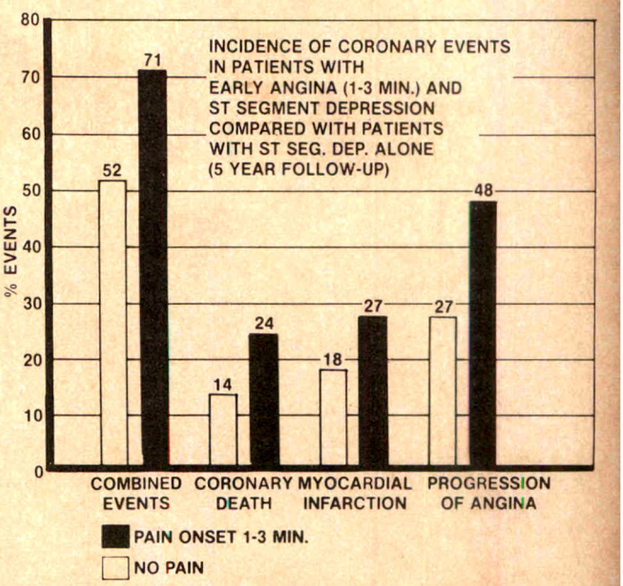


FIGURE 4. Bar graph illustrating the incidence of separate and combined coronary events at 5 year follow-up in subjects with or without chest pain during the first 3 minutes (MIN.) of exercise testing.ST SEG. DEP. = S-T segment depression.

7 years, the incidence rate of coronary events rose to 76 percent in patients with pain and to 48 percent in those free of pain during the test (Fig. 3). Coronary death and progression of angina also doubled over a 7 year period in patients with angina during the abnormal treadmill test.

Onset of angina: Coronary events were twice as frequent in patients with early onset of anginal pain at a light work load (1 to 3 minutes of testing, 4 metabolic equivalents = METS) of exercise testing as in those with pain at a heavy work load (7 minutes of testing, 8 to 9 METS), a load very near the peak capacity of most subjects. Subjects with angina induced at a light work load (1 to 3 minutes) demonstrated slightly more than double the incidence of coronary events found in subjects with angina induced by a heavy work load (Fig. 4 to 6).

Age and sex: Men aged 41 to 50 years with treadmill-induced angina had a tripled incidence of coronary

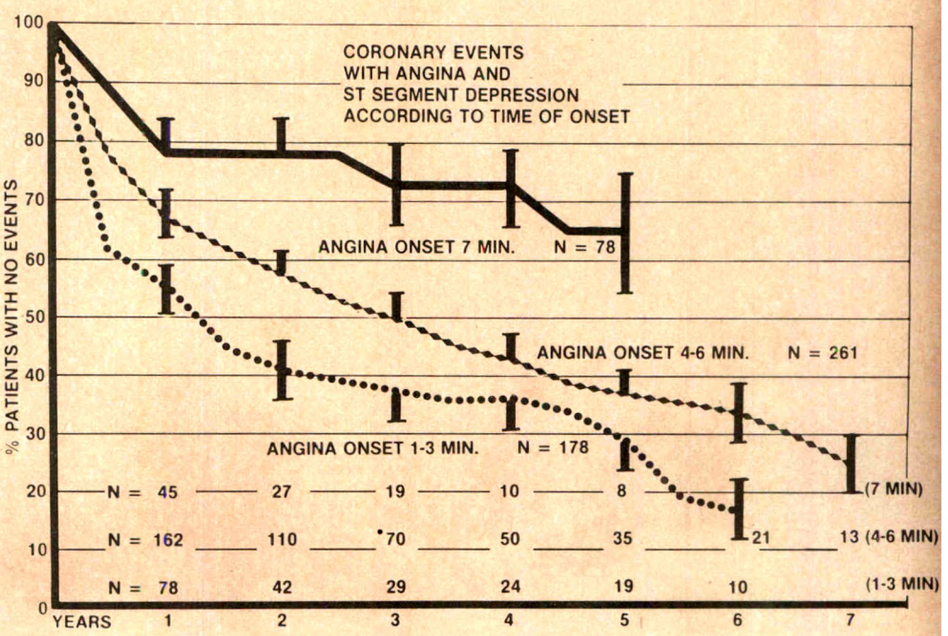


FIGURE 5. Life table comparing the incidence of coronary events in relation to angina induced by a light, moderate and heavy work load during exercise testing. MIN = minutes; N = number of patients.

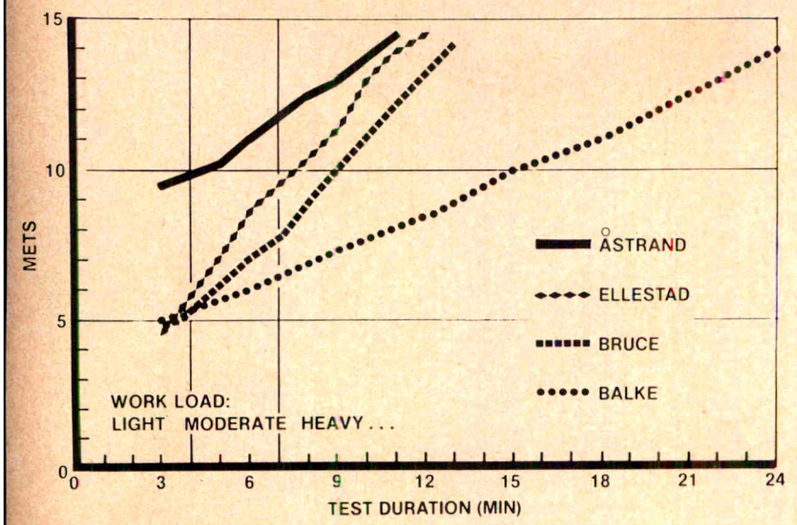


FIGURE 6. Comparison of four exercise protocols according to metabolic equivalents (METS) of the actual work load. MIN. = minutes.

events compared with their counterparts without angina (Fig. 7 and 8). These men with angina during the positive test had an 18 percent incidence rate of myocardial infarction during the 5 year period compared with a 4 percent incidence rate in the men without angina (Fig. 9). Thus, men aged 41 to 50 years having angina during the test had a more than quadrupled incidence of myocardial infarction compared with their counterparts who were free of pain during the test; the incidence of other coronary events (coronary death and progression of angina) doubled for the men in this age group who had pain during the test.

The questionnaire disclosed a history of chest pain in 93 percent of the women studied, compared with only 67 percent of the men; however, in women the occurrence of pain during the test was not correlated with an increased incidence of coronary events after 3 years. Thus, chest pain during the abnormal treadmill test was a less useful prognosticator of future coronary events in women than in men (Fig. 10).

Angiographic correlations: Coronary artery disease was considered angiographically significant when there was 50 percent or greater narrowing of the luminal diameter of a diseased vessel. Angiography, performed in 295 patients, revealed that an abnormal treadmill test for ischemia had a 64 percent true positive rate for significant coronary artery disease. This true positive rate increased to 85 percent (91 percent in men, 17 percent in women) among the 197 patients who had angina during the abnormal stress test. At a light work load (4 METS), the time of onset of S-T segment depression has unique significance in evaluating the severity of

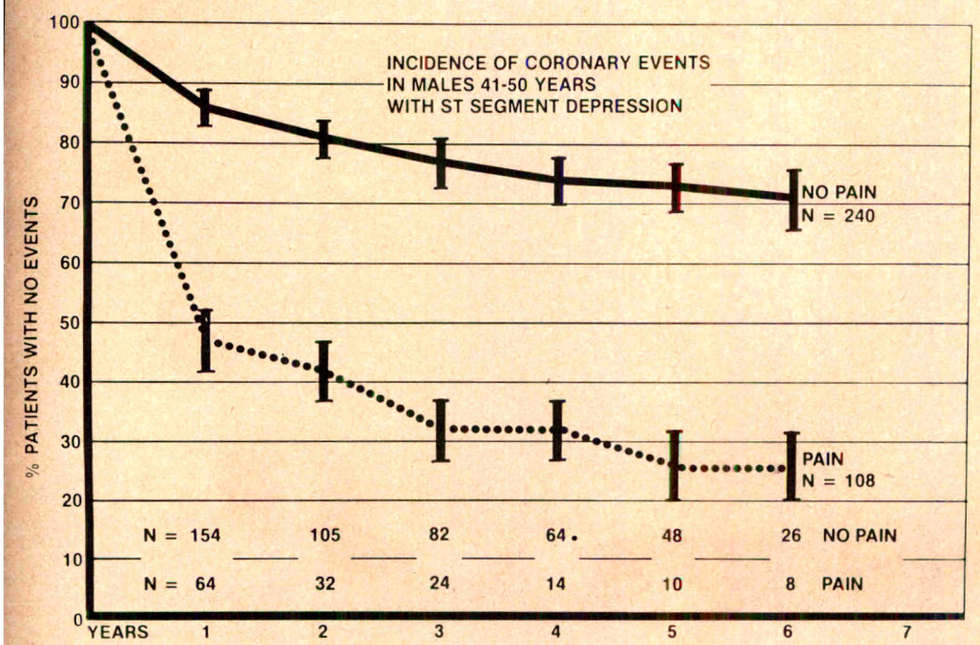
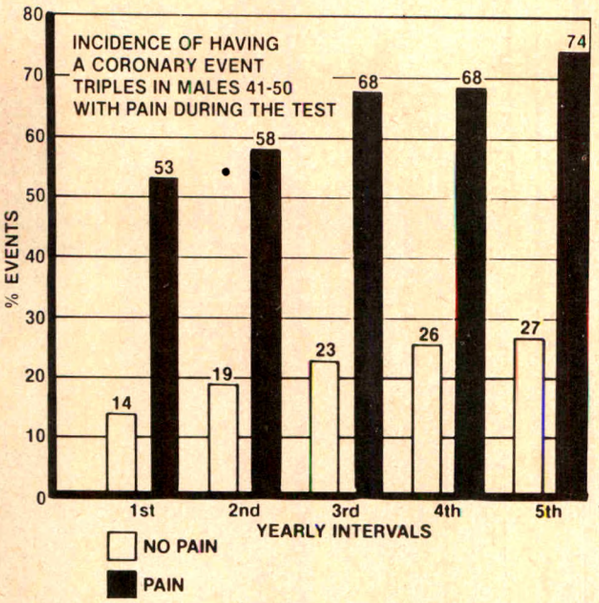


FIGURE 7. Life table illustrating the incidence of coronary events in men aged 41 to 50 years according to the presence or absence of chest pain during exercise testing with significant S-T segment depression. N = number of patients.



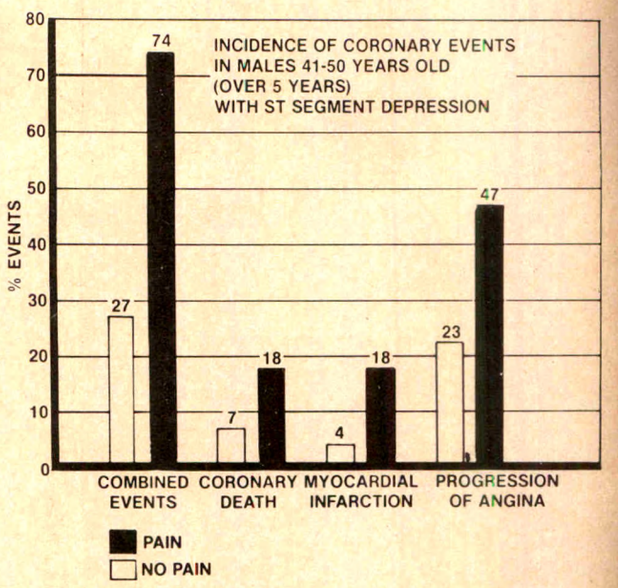


FIGURE 8 (left). Bar graph demonstrating that in men aged 41 to 50 years the incidence of coronary events triples when pain occurs during exercise testing.

FIGURE 9 (right). Bar graph depicting the incidence of separate and combined coronary events at 5 years in men aged 41 to 50 years according to the presence or absence of chest pain during exercise testing.

disease, as previously reported by Ellestad.[8] In our study, subjects with both S-T depression and pain at a light work load tended to have more coronary events than those with S-T depression and no pain. Angina occurring early in the protocol had more significance than asymptomatic S-T depression. When angina occurred during a heavy work load (8 to 9 METS), the incidence of coronary events was essentially the same as with positive tests for ischemia (Fig. 1 and 5).

Discussion

Predictive value of angina during exercise testing: In our subjects with a positive test by electrocardiogram, the presence of angina predicted a large inci-

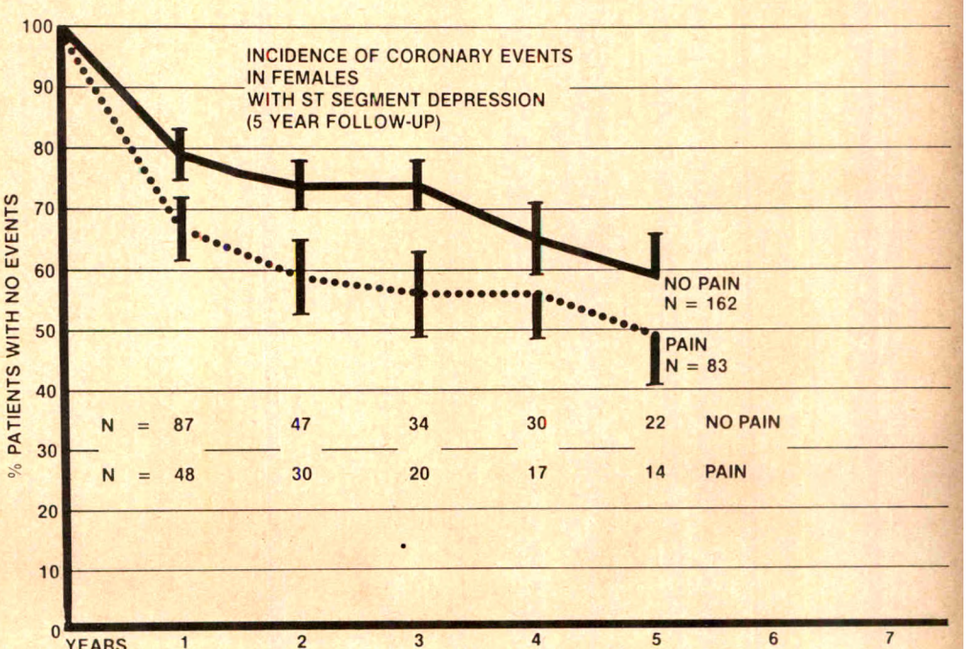


FIGURE 10. Life table illustrating the incidence of coronary events at 5 years in all women according to the presence or absence of chest pain with significant S-T segment depression during exercise testing. N = number of patients.

dence of later coronary events. Men aged 41 to 50 years with angina during a positive stress test had a 3- and 4-fold greater incidence of coronary events than similarly aged men without exercise-induced angina. These middle-aged men with exercise-induced pain may require more careful attention to control of risk factors and management of disease. Angina during exercise testing was a less accurate indicator of coronary disease in women. The examiner identified chest pain as angina on the basis of the patient's description, its duration, location, response to nitroglycerin and other factors that are partly subjective. Although chest pain is more likely to be of noncoronary origin in women than in men, our results suggest that our ability to categorize it is of less significance in women. Myocardial ischemia of noncoronary origin is also more common in women than in men.

All patients in our study who had angina during a positive exercise test had a doubled incidence of coronary events. Angina during exercise testing increased the sensitivity rate for angiographic coronary disease to 85 percent of all subjects with an abnormal stress test for ischemia. Weiner et al.[7] reported 91 percent true positive results for coronary artery disease when subjects had pain during exercise testing. The difference in results in their study may well be due to inherent differences in patient selectivity since our study, by design, included many subjects known or highly likely to have advanced coronary artery disease as well as many believed to be perfectly normal.

As noted in the life table figures, the majority of coronary events occurred during the first year of follow-up study. Therefore, we believe that exercise testing is a valuable aid in determining the risk of a subsequent coronary event in symptomatic patients and those highly likely to have ischemia. The possibility that asymptomatic subjects would manifest S-T segment depression and angina during exercise is remote, although it cannot be excluded. We believe that the patients in our study would be representative of a patient population referred to a moderate to large community hospital for exercise testing to evaluate suspected ischemia. Surgical patients were excluded and the types of treatment were not taken into consideration.

Other factors influencing evaluation of the stress test: Although the study was constructed to evaluate the contribution of angina to the evaluation of treadmill data, other clinical factors are also important. It must be emphasized that a considerable number of subjects with severe coronary disease do not have pain on testing. The time of onset of S-T segment depression, the magnitude of S-T depression, S-T segment contours, achieved heart rate response, blood pressure response and age have also been shown to have significance in predicting the outcome of patients with exercise-induced S-T segment depression. These and other clinical findings should be evaluated when determining the significance of a stress test.

Clinical implications: The presence of chest pain during treadmill testing increases the sensitivity of the test more accurately than its absence. Life table data demonstrate that the presence of anginal pain during the test identifies a cohort of high risk patients in terms of subsequent coronary events such as progression of angina, myocardial infarction and death. This study has unique significance in patients with anginal pain of early onset manifested at light to moderate work loads as compared with patients with pain at higher work loads. It also has more significance in younger than older subjects.

Acknowledgment

We are especially grateful to the attending physicians of Memorial Hospital Medical Center who helped us obtain follow-up data on the subjects tested, and to Lee Richard, our computer programmer, who made it possible to analyze the data in a meaningful way. We also thank John Manning, who helped us assemble the data and prepare the tables, and Fritzie Cohn for the preparation of the manuscript.

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Plasma Norepinephrine in Congestive Heart Failure

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Resting plasma concentrations of norepinephrine, dopamine-beta-hydroxylase enzyme activity and peripheral blood lymphocyte beta adrenergic receptor sensitivity to isoproterenol as reflected in cyclic 3′,5′-adenosine monophosphate (cAMP) generation were studied in patients with congestive heart failure due to atherosclerotic heart disease or to congestive cardiomyopathy or hypertensive cardiovascular disease. Systolic time intervals were also measured in nonhypertensive patients and correlated with the plasma norepinephrine concentration. Control patients were hospital employees without a previous history of heart disease or hypertension, and were matched for age to eliminate the effect of increasing age on the plasma norepinephrine concentration.

The results of this study clearly demonstrate that the plasma norepinephrine concentration is directly related to the degree of left ventricular dysfunction in patients with congestive heart failure. When the systolic time intervals were correlated with the plasma norepinephrine levels, a significant prolongation of the preejection period was observed with progressively increasing plasma concentrations of norepinephrine. The reverse was true for the left ventricular ejection time, which demonstrated a significant inverse relation with the plasma norepinephrine concentration. The ratio of the preejection period to the left ventricular ejection time, which is a reflection of left ventricular function, significantly increased with increasing levels of plasma norepinephrine. In addition, plasma lymphocytes from patients with the greatest degree of left ventricular dysfunction failed to generate normal amounts of cAMP after beta adrenergic receptor stimulation with isoproterenol. It is suggested that beta adrenergic receptors are desensitized in these patients and that this desensitization contributes to the observed alterations in myocardial contractility.

The role of the sympathetic nervous system remains poorly understood in both compensated and decompensated congestive heart failure, although an augmentation of sympathetic nervous activity in heart failure has previously been described.[1] An increase in impulse traffic in sympathetic nerves leads to the release of the endogenous neurotransmitter norepinephrine and its synthetic enzyme dopamine-beta-hydroxylase, and it has been proposed that the release of the latter enzyme might be used clinically to reflect changes in overall sympathetic nervous activity.[2] Release of norepinephrine is followed by the stimulation of adrenergic receptors, either in the heart or in other sympathetic beds throughout the body. This sequence of events is capable of increasing both contractility and the frequency of contractions of cardiac muscle[3] and is also capable of producing many extracardiac manifestations. These are reflected in a reduction of cutaneous blood flow,[4] the presence of venoconstriction,[5–7] elevation of renal vascular resistance[8] and augmentation of plasma catecholamines during exercise[9] associated with an increase in the urinary excretion of catecholamines.[1]

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The augmentation in plasma norepinephrine concentration in patients with congestive failure during exercise was originally reported by Chidsey et al.[9] and was interpreted as an indication of an increased sympathetic outflow, providing an important cardiovascular supportive mechanism in these patients. Associated with this increased noradrenergic activity was an apparently normal adrenal medullary catecholamine release process, reflected in normal plasma and urinary levels of epinephrine.[1,9] This implied that sympathetic beds other than the adrenal medulla were responsible for this augmentation of noradrenergic activity. Many investigators[10–13] have reported a depletion of myocardial norepinephrine in congestive failure, both in human subjects and in experimental animal models. The mechanism of this depletion of the cardiac sympathetic neurotransmitter has not yet been elucidated. It remains to be established whether prolonged increases in cardiac sympathetic activity could lead to an exhaustion of the noradrenergic stores of the heart.[1] It is clear, however, that cardiac sympathetic nerves release norepinephrine and dopamine-beta-hydroxylase from their nerve terminals and that norepinephrine interacts with cardiac beta receptors, which are the sites for the modulation of intracell biochemical events that utilize cyclic 3′,5′-adenosine monophosphate (cAMP) as the second messenger.[14]

The search for an appropriate human in vitro model with which to study the beta adrenergic-cAMP relation led Scott[15] to demonstrate the stimulation of adenylate cyclase from human lymphocytes by epinephrine in broken cell preparations. Parker et al.[16] then studied peripheral blood lymphocytes from patients with bronchial asthma in search of possible alterations in cyclic 3′,5′-cAMP metabolism. Cells from asthmatic patients, at the time that the asthmatic condition was most severe, were found to have a highly significant decrease in their cAMP response to beta adrenergic agents as compared to normal control cells. These same cells, however, had an unaltered response to stimulants that activate adenylate cyclase by mechanisms other than through the beta receptor, thus demonstrating that the defect in catecholamine responsiveness was at the level of the beta adrenergic receptor.

The present study was undertaken to reinvestigate the functional activity of the sympathetic nervous sys-

TABLE I

Characteristics of 19 Patients Grouped According to Severity of Cardiac Failure on Admission

Case no.	Age (yr) & Sex	Race	HR	BP	Diagnosis	NYHA Class Adm	NYHA Class Dis	NE Adm	NE Dis	DBH Adm	DBH Dis
					Class II						
1*	61M	W	70	232/108	HCVD	II	II	0.28	0.90	853	604
2*	69F	W	50	160/80	HCVD	II	II	1.2	0.33	382	350
3	75F	W	112	110/60	ASHD	II	I	0.65	0.41	589	467
4	54M	B	76	134/88	ASHD	II	II	0.51	0.56	415	430
Mean	64.7		77					0.66	0.55	560	463
± SEM	4.6		13					0.19	0.13	108	53
					Class III						
5	63F	B	100	150/92	HCVD	III	II	1.80	0.24	236	203
6*	49F	B	100	180/130	HCVD	III	II	0.68	0.23	0	0
7	56F	B	80	120/80	HCVD	III	II	2.30	0.77	113	59
8*	60F	B	62	190/130	HCVD	III	II	1.00	0.54	471	426
9	71M	B	88	130/90	CCM	III	III	1.20	1.50	515	387
10	38M	W	80	100/80	ASHD	III	II	0.82	0.51	331	226
11	60M	B	62	112/82	CCM	III	II	2.50	0.60	243	189
Mean	56.7		81.7					1.47	0.63	273	213
± SEM	4.0		6.0					0.28	0.16	70	59
					Class IV						
12*	61F	B	76	150/76	HCVD	IV	II	0.25	0.37	409	336
13*	58M	B	92	190/110	HCVD	IV	II	1.20	0.25	881	626
14	57M	B	96	100/60	ASHD	IV	II	2.00	0.24	329	714
15	75F	W	84	160/78	ASHD	IV	III	2.20	2.40	457	349
16	48M	W	110	120/70	ASHD	IV	III	1.50	1.10	268	569
17†	26M	B	100	112/70	CCM	IV	IV	3.70	1.90	7	0
18	56F	W	70	120/70	CCM	IV	IV	0.88	1.40	165	321
19	56F	B	76	100/80	CCM	IV	III	2.10	1.40	209	403
Mean	54.6		88					1.73	1.12	341	415
± SEM	4.9		5					0.37	0.29	93	79
Total Mean	57.5		83					1.41	0.82	362	350
± SEM	2.7		4					0.20	0.15	55	46

* On methyldopa.
† Died.
Adm = admission; ASHD = atherosclerotic heart disease; B = black; BP = blood pressure (mm Hg) on admission; CCM = congestive cardiomyopathy; Dis = discharge; DBH = dopamine-beta-hydroxylase (nanomole/ml per hour); F = female; HR = heart rate (beats/min) on admission; HCVD = hypertensive cardiovascular disease; NE = norepinephrine (ng/ml); NYHA Class = New York Heart Association functional class; SEM = standard error of the mean; W = white.

tem, and its relation to compensated and decompensated heart failure. Plasma norepinephrine and dopamine-beta-hydroxylase levels were measured to assess sympathetic neuronal activity. The ability of peripheral blood lymphocytes to generate cAMP in the presence of beta receptor agonists was tested as a reflection of beta adrenergic receptor sensitivity. Systolic time interval measurements were used as a noninvasive technique for estimating changes in cardiac contractility and were correlated with the plasma catecholamine levels. The results of this study suggest that plasma levels of norepinephrine correlate very well with the functional cardiac status of patients with congestive heart failure. In addition, grossly elevated levels of plasma norepinephrine occur with chronic cardiac decompensation, and this may be associated with the development of desensitization of cardiac beta adrenergic receptors.

Study Subjects

Nineteen patients were included in this study. Six patients had atherosclerotic heart disease, and five patients were diagnosed as having congestive cardiomyopathy. Eight patients had hypertensive cardiovascular disease, and six of these patients were taking at least 750 mg/day of methyldopa (Table I). This medication was being taken at the time of admission to the study, and was continued throughout the observation period. All patients received a digitalis preparation (digoxin), a diuretic agent (furosemide or hydrochlorothiazide) and a potassium supplement both before entry into the study and during the course of the observation period. The functional cardiac status at the time of admission of each patient, as described by the New York Heart Association Criteria Committe,[17] ranged from slightly compromised to severely compromised (Class II–IV).

The physiologic cardiac diagnosis of left ventricular failure required one or more of the following criteria: (1) radiologic evidence of a sudden increase in left ventricular size, (2) a ventricular third sound or summation gallop sound over the left ventricle in the absence of mitral regurgitation, (3) angiocardiographic evidence of a dilated left ventricle and a cardiac output below 2.7 liters/min per m^2, or (4) manifestations of pulmonary congestion or pulmonary edema in the presence of a large left ventricle.

Patients in the study ranged in age from 26 to 75 years, with a mean age of 50.1. Ten of the patients were women, and nine were men. Control patients were hospital employees without any prior history of hypertension or heart disease. Control patients were matched for age to eliminate the effect of increasing age on the plasma norepinephrine concentration.[18]

Protocol: Blood was obtained from an antecubital vein while the subjects were supine and at rest for at least 5 minutes; indwelling catheters were not utilized. Blood specimens for norepinephrine and dopamine-beta-hydroxylase measurements and lymphocyte purification, were obtained from patients at the time of admission to the study, and every third morning between 7:00 and 8:00 AM with the patient at rest. Measurements of the blood pressure, heart rate and systolic time intervals were simultaneously obtained with the subject at rest and in the supine position. Systolic time interval measurements were taken as close to the day of admission as possible. Repeat measurements of time intervals were performed randomly throughout the hospital course. In all cases, systolic time interval measurements were always taken on the same morning during which a plasma specimen was obtained for the measurement of norepinephrine and dopamine-beta-hydroxylase. Measurements were terminated when the patients demonstrated improvement in clinical signs and symptoms of congestive heart failure for 96 or more hours, had demonstrated a constant body weight or necessitated a change in the therapeutic regimen. At least 7 days of hospitalization was required for patient inclusion in this study.

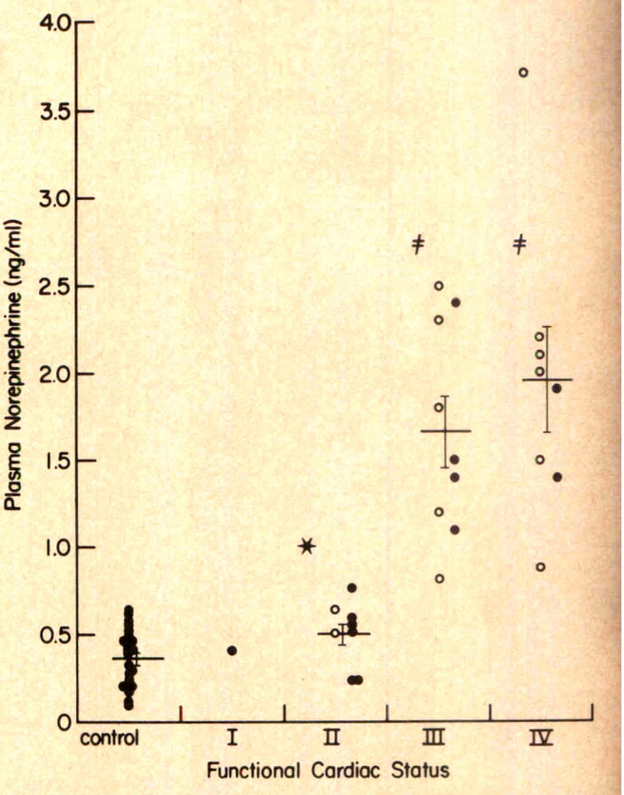

FIGURE 1. Functional cardiac status (New York Heart Association class) versus plasma norepinephrine concentrations in control subjects and in patients with congestive heart failure. **Open circles** represent admission values and **closed circles** represent discharge values for concentrations of plasma norepinephrine (no. = 13 for each group). Control values are as indicated (no. = 23). The mean ± standard error of the mean is indicated by the **solid bar** for each functional class. * = probability value (P) <0.001 compared with patients in classes III and IV; ≠ = P <0.001 compared with control period.

Methods

Plasma norepinephrine concentration was measured by the method of Henry et al.[19] Blood specimens were collected in heparinized tubes, and immediately placed on ice. The plasma was separated by centrifugation at 4° C within 30 minutes of obtaining the specimen. The plasma was then frozen and stored at −70 °C until the time of analysis. The isotopic enzymatic method involves the conversion of norepinephrine to ^{3}H-epinephrine, by the transfer of a ^{3}H-methyl group from ^{3}H-S-adenosylmethionine to the primary amine group of norepinephrine. The reaction is catalyzed by the enzyme phenylethanolamine-N-methyltransferase, and concentrations are reported in nanograms (ng) per milliliter (ml). Furosemide, digoxin and hydrochlorothiazide added to the assay mixture in concentrations equal to maintenance blood levels had no effect on the measurement of plasma norepinephrine concentration. In the case of methyldopa, concentrations from 5 to 20 μg/ml produced an apparent in-

crease above control levels in the measurable norepinephrine from 0.32 to 0.94 ng/ml, respectively.

Dopamine-beta-hydroxylase was measured with the radioisotopic method of Weinshilboum and Axelrod[20]; one unit of hydroxylase enzyme activity represents the formation of 1 nmol of phenylethanolamine product per milliliter of plasma per hour.

Lymphocytes were purified from whole blood on a Ficoll-Hypaque gradient at 4° C as described by Böyum.[21] Purified cells were washed and resuspended in Krebs-Henseleit buffer at pH 7.4. Cells were then incubated in the presence of 5 millimolar isoproterenol for either zero or 10 minutes at 37° C as described by Parker and Smith,[16] and the incubation was terminated by the addition of trichloroacetic acid to a final concentration of 7 percent. After ether extraction, the level of cyclic 3′,5′-adenosine-monophosphate (cAMP) was determined by radioimmunoassay as described by Steiner et al.[22] Results are expressed as picomoles (pM) cAMP/10^6 cells.

The durations of the phases of left ventricular systole were measured from simultaneous recordings of the electrocardiogram, phonocardiogram and carotid arterial pulse tracing as previously described by Weissler et al.[23] The following phases were measured directly: (1) the total electromechanical systolic interval (Q-S_2), (2) the left ventricular ejection time interval (LVET), and (3) the interval between the first and second heart sounds (S_1-S_2). The preejection period (PEP) interval was calculated from these measurements. The rate-corrected systolic time intervals are also reported.

Data were analyzed with use of Student's *t* test for individual and group differences and paired data analysis, and by the method of least squares for calculating regression coefficients as described by Delaunois.[24]

Results

Plasma norepinephrine concentration and degree of cardiac failure: Identifying data for all patients included in this study are summarized in Table I. Patients are represented in three groups on the basis of their functional cardiac status on admission. The plasma norepinephrine concentrations exhibit a progressive increase as patients demonstrate continued left ventricular functional deterioration. Although all three groups had plasma norepinephrine levels that were significantly different from the control value at the time of admission, plasma concentrations of patients in classes III and IV remained significantly elevated above control level at the end of the observation period ($P < 0.001$ for cardiac status III and IV, respectively). This finding is also presented graphically in Figure 1, but this figure includes only patients not treated with methyldopa. Whether at the beginning or the end of the observation period, the plasma norepinephrine level was found to correlate directly with the functional cardiac status and reflected the degree of cardiac decompensation.

Plasma dopamine-beta-hydroxylase enzymatic activity: No significant differences in this activity were observed in any of the patients in the study, although

TABLE II

Characteristics of Control Subjects

Case no.	Age (yr) & Sex	DBH	NE	HR	BP	MAP	Q-S_2	LVET	PEP	PEP/LVET	Q-S_2I	LVETI	PEPI
1	58M	691	0.56	89	118/70	86	388	283	105	0.37	575	434	141
2	34F	638	0.49	72	102/68	80	401	297	104	0.35	545	412	133
3	36F	. . .	0.11	71	122/78	93	391	279	112	0.40	533	393	140
4	47F	0	0.45	74	154/98	117	398	292	106	0.36	546	410	136
5	48F	1271	0.62	67	108/68	82	384	298	86	0.29	518	405	113
6	23F	460	0.64	85	126/74	92	348	271	77	0.28	518	407	111
7	48F	1192	0.24	81	120/70	87	376	300	76	0.25	538	430	108
8	44F	223	0.46	72	112/72	86	380	278	102	0.37	524	393	131
9	41F	575	0.27	53	124/76	92	466	358	108	0.30	572	443	129
10	60F	398	0.29	80	138/86	104	398	286	92	0.32	538	414	124
11	25M	. . .	0.22	60	126/82	97	404	298	106	0.36	530	400	130
12	44F	902	0.21	66	120/78	93	395	300	95	0.32	527	406	121
13	60M	9	0.21	75	120/85	97	374	285	89	0.31	532	413	119
14	53M	921	0.32	86	128/64	86	391	286	105	0.37	572	432	139
15	54F	192	0.57	66	110/60	77	428	326	102	0.31	560	432	128
16	62F	713	0.45	71	130/80	97	408	305	103	0.33	548	417	131
17	29M	461	0.10	86	128/82	98	35	263	88	0.33	532	409	122
18	30M	1229	0.41	78	115/76	90	374	266	108	0.41	538	399	139
19	32M	277	0.41	50	130/82	98	425	340	85	0.25	530	425	105
20	30F	290	0.40	108	124/82	96	347	278	69	0.25	568	451	112
21	32 F	705	0.18	62	110/70	84	417	320	97	0.30	541	419	122
22	54F	665	0.53	76	118/68	85	404	308	96	0.31	556	430	126
23	54M	124	0.43	81	118/84	96	373	284	86	0.31	543	422	121
Total Mean	43.4	568	0.37	74.0		91.0	391.0	295.0	96.0	0.32	543.0	417.0	125.0
± SEM	2.6	83	0.03	2.6		1.9	5.7	4.8	2.4	0.01	3.6	3.2	2.2

BP = blood pressure (mm Hg); DBH = dopamine-beta-hydroxylase (nanomol/ml per hour); HR = heart rate (beats/min); LVET = left ventricular ejection time (msec); LVETI = left ventricular ejection time index; MAP = mean arterial pressure (mm Hg); NE = norepinephrine (ng/ml); PEP = preejection period (msec); PEPI = preejection period index; Q-S_2 = total electromechanical systole (msec); Q-S_2I = total electromechanical systolic index.

those patients exhibiting a more severe degree of cardiac decompensation tended to have lower admission values of dopamine-beta-hydroxylase enzymatic activity (Table I).

Systolic time intervals: Measurements for the control subjects and for patients with heart failure are summarized in Tables II, III and IV. Values are reported only for patients not receiving methyldopa. The values for plasma norepinephrine concentration, blood pressure and heart rate represent measurements made the same morning as the systolic time intervals. The data of patients with heart failure are grouped in Table III according to the functional cardiac status of the patient at the time the measurement was performed and include the mean values of each systolic interval for each functional status. A regression matrix of the systolic intervals as a function of plasma norepinephrine concentration and heart rate both before and after rate correction is seen in Table IV.

Analysis of the data in Tables II and III reveals a highly significant inverse relation between the duration of the electromechanical systolic interval ($Q\text{-}S_2$) and the heart rate in both control subjects and in patients with heart failure ($r = -0.79$, $P < 0.001$; $r = 0.81$, $P < 0.001$, respectively. See also Table IV). This is in agreement with previously published data of Lombard and Cope[25] and of Weissler et al.[23] Patients with heart failure had a significantly shorter $Q\text{-}S_2$ interval than the control subjects ($P < 0.001$) and also had a proportional increase in their heart rate. This decrease in the $Q\text{-}S_2$ interval with respect to the heart rate was caused by a significant decrease in the left ventricular ejection time, and although the latter was inversely related to the heart rate, the interval in patients with cardiac decompensation was markedly decreased compared with that in control subjects for any given heart rate ($P < 0.001$).

The relation between the preejection period and the heart rate for patients with failure and for control subjects is shown in Figure 2. Whereas neither of these regression lines demonstrate a significant correlation, the slopes have opposite absolute signs and are significantly different from each other when compared by Student's t test ($P < 0.005$). It would therefore appear that the effect of increasing heart rate on the preejection period in patients with heart failure is a tendency toward prolongation, an effect opposite from that observed in subjects with normal left ventricular function.

TABLE III

Systolic Time Intervals in Patients With Cardiac Failure Grouped According to Functional Class on Day of Measurements

Case no.	Age (yr) & Sex	Diagnosis	NE	HR	$Q\text{-}S_2$ (msec)	LVET	PEP (msec)	PEP/LVET	BP	MAP	$Q\text{-}S_2I$	LVETI	PEPI
						NYHA Class II							
4	54M	ASHD	0.51	75	361	256	105	0.41	108/88	95	519	384	135
10	38M	ASHD	0.61	92	348	210	138	0.66	90/70	76	541	366	175
3	75F	ASHD	0.65	104	352	241	111	0.46	140/80	100	560	407	153
"			0.42	88	359	252	107	0.42	160/90	114	535	393	142
"			0.41	79	354	254	100	0.39	130/60	84	512	380	132
Mean	63.0		0.52	88	354	243	112	0.47		93	533	386	147
± SEM	7.5		0.05	5	2	9	7	0.05		9	9	7	8
						Class III							
5	63F	HCVD	1.76	92	323	168	155	0.92	126/70	86	507	315	192
7	56F	HCVD	2.30	85	320	193	127	0.66	102/74	84	490	329	161
10	38M	ASHD	1.39	96	298	191	107	0.56	98/74	80	500	354	145
19	56F	CCM	1.37	124	291	173	118	0.68	90/70	77	537	371	168
Mean	53.3		1.71	99	308	181	127	0.71		83	509	342	167
± SEM	5.4		0.22	9	8	6	10	0.08		3	10	13	10
						Class IV							
19	56F	CCM	2.08	97	322	202	120	0.59	100/80	87	516	357	159
17	26M	CCM	3.72	108	310	176	134	0.76	90/40	57	537	360	177
"			1.01	115	302	181	121	0.67	110/90	97	544	377	167
"			0.84	110	312	187	125	0.67	94/70	78	543	374	169
"			3.40	118	284	155	129	0.83	110/68	82	532	356	176
14	57M	ASHD	2.00	91	345	214	131	0.61	86/64	71	536	369	177
16	48M	CCM	1.54	97	313	191	122	0.64	120/80	94	517	356	161
Mean	37.9		2.08	105	313	187	126	0.68		81	532	364	169
± SEM	5.7		0.42	4	7	7	2	0.03		5	4	3	3
Total													
Mean	49.7	1.50	98	325	203	122		0.62		85	527	366	162
± SEM	4.5	0.25	4	6	8	4		0.03		3		6	4

BP = blood pressure (mm Hg); HR = heart rate (beats/min); LVET = left ventricular ejection time (msec); LVETI = left ventricular ejection time index; MAP = mean arterial pressure (mm Hg); NE = norepinephrine (ng/ml); PEP = preejection period (msec); PEPI = preejection period index; $Q\text{-}S_2$ = total electromechanical systole (msec); $Q\text{-}S_2I$ = total electromechanical systolic index.

TABLE IV

Regression Matrix of Norepinephrine and Heart Rate Versus Systolic Time Intervals in Patients With Cardiac Failure

	Q-S_2		LVET		PEP		PEP/LVET	
	Control	CHF	Control	CHF	Control	CHF	Control	CHF
NE vs	−0.03	−0.59[3]	0.02	−0.68[2,4]	−0.10	0.50[1,3]	−0.11	0.67[2,4]
HR vs	−0.79[5]	−0.81[5]	−0.74[5]	−0.70[5]	−0.40	0.25		
	Q-S_2I		LVETI		PEPI			
	Control	CHF	Control	CHF	Control	CHF		
NE vs	0.11	−0.17	0.15	−0.54[3]	−0.04	0.56[1,3]		

[1] $P < 0.01$ compared with control; [2] $P < 0.001$ compared with control; [3] significant correlation ($P < 0.05$); [4] significant correlation ($P < 0.01$); [5] significant correlation ($P < 0.001$).

CHF = congestive heart failure; HR = heart rate; LVET = left ventricular ejection time; LVETI = left ventricular ejection time index; NE = norepinephrine; PEP = preejection period; PEPI = preejection period index; Q-S_2 = total electromechanical systole; Q-S_2I = total electromechanical systolic index.

Relations between the systolic time intervals and the plasma norepinephrine concentration are depicted in Figures 3 and 4 and Table IV, with Figure 3 depicting intervals that have been corrected for rate. In control subjects, no correlation is noted between the plasma norepinephrine concentration and the Q-S_2, left ventricular ejection time and preejection period with or without rate correction (Table IV). The Q-S_2 interval in patients with left ventricular dysfunction was inversely related to the plasma norepinephrine concentration ($P < 0.001$) as a result of a marked shortening of the left ventricular ejection time (Fig. 3A). This finding is consistent with a progressive reduction in stroke volume in the presence of increasingly higher levels of circulating catecholamine in patients with cardiac decompensation. The opposite effect was noted with respect to the preejection period (Fig. 3B). A prolongation of the preejection period was observed in association with elevated plasma norepinephrine levels in heart failure ($r = 0.50$, $P < 0.05$), an effect that was similar to the regression of PEP on heart rate (Fig. 2). A comparison of the preejection period (PEP) and left ventricular ejection time (LVET) before and after correction for heart rate (Table IV) demonstrated that the statistical significance of the respective positive and inverse correlations was maintained.

An analysis of changes in the ratio of the PEP/LVET intervals with respect to the plasma norepinephrine concentration is seen in Figure 4. The positive correlation ($r = 0.67$) is significant and demonstrates a highly significant difference from the control value ($P < 0.001$). In addition, those patients in functional classes I and II had a plasma norepinephrine concentration of less than 0.70 ng/ml, which would not be considered outside the range of normal values for this laboratory. On the other hand, patients in classes III and IV having the

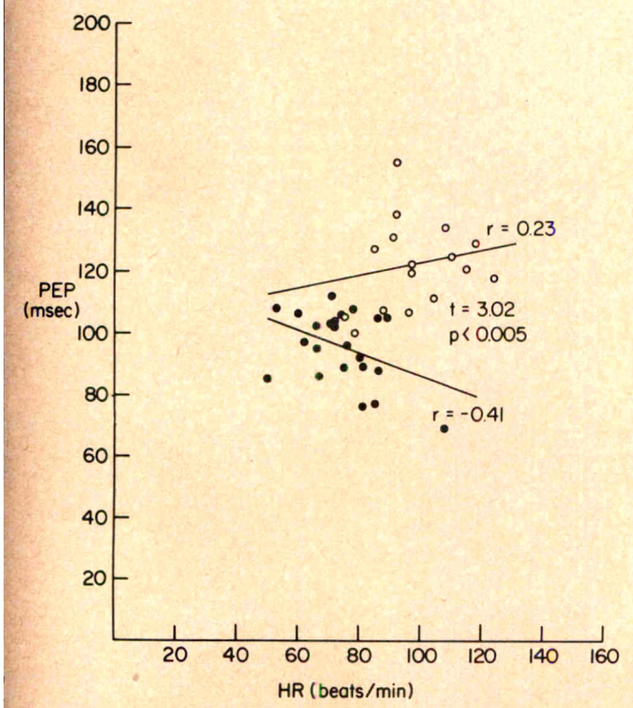

FIGURE 2. Preejection period (PEP) as a function of heart rate (HR) in control subjects and in patients with congestive heart failure. Control subjects represented by **closed circles** (no. = 23), patients with failure by **open circles** (no. = 16). The correlation coefficients (r) for each regression line are not significant. A comparison of the slopes of the two lines by Student's *t* test (t) is highly significant ($P < 0.005$).

TABLE V

Cyclic 3′,5′-adenosine monophosphate (cAMP) Generation After Exposure to 5 millimolar Isoproterenol in Lymphocytes From Normal Subjects and Patients With Functional Class III and IV Heart Failure

Incubation Time (min)	Cases (no.)	Lymphocyte cAMP (pM/10^6 cells ± SEM) 0 Minutes	10 Minutes
Control	21	1.24 ± 0.28	17.72 ± 1.43
CHF (class III + IV)	17	0.78 ± 0.18†	5.89 ± 0.94*

* $P < 0.001$ compared with control.

† $P > 0.1$ compared with control.

CHF = congestive heart failure; pM = picomoles; SEM = standard error of the mean.

highest PEP/LVET ratios, also had the highest plasma norepinephrine concentrations.

Relation between mean arterial pressure and plasma norepinephrine level (Fig. 5): In patients with left ventricular dysfunction, the mean arterial pressure was inversely related to plasma norepinephrine ($r = -0.59$, $P < 0.05$). However, there was no significant relation between the mean arterial pressure and the plasma norepinephrine level in the control group. Our data support the hypothesis that prolongation of the preejection period in these patients is not the result of norepinephrine-induced increases in afterload but reflects the reduction of left ventricular contractility.

Beta adrenergic receptor mediated generation of cAMP in lymphocytes: The values from both control subjects and patients with heart failure are shown in Table V. A highly significant decrease in the amount of cAMP generated after incubation of lymphocytes with 5 millimolar isoproterenol for 10 minutes is observed in the heart failure group ($P < 0.001$).

Discussion

Our results demonstrate that plasma levels of norepinephrine are elevated in resting patients with incipient and frank left ventricular decompensation. This finding is in agreement with earlier reports that plasma and urinary levels of norepinephrine were elevated in patients with congestive heart failure both at rest and during exercise,[1,9] and also elevated in various experimental animal models of right and left ventricular

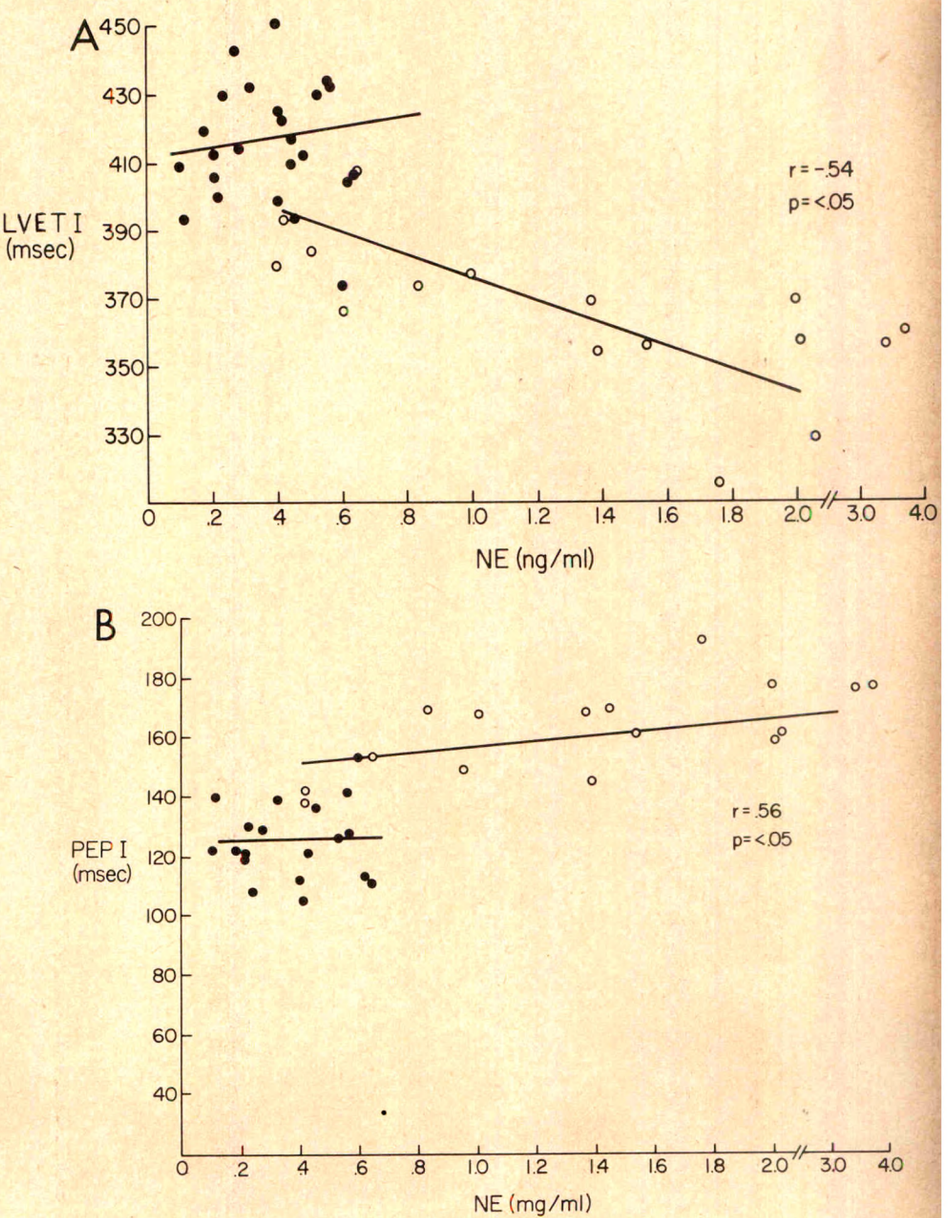

FIGURE 3. A, relation between rate-corrected left ventricular ejection time (LVETI) and plasma norepinephrine concentration (NE). Control subjects are represented by **closed circles** (no. = 23), patients with left ventricular failure by **open circles** (no. = 16). The correlation coefficient (r) of the regression line for the patients with failure is indicated and is significant ($P < 0.05$). **B,** relation between the rate-corrected preejection period (PEPI) and plasma norepinephrine concentration (NE). Patients with heart failure are represented by **open circles** (no. = 16), control subjects by **closed circles** (no. = 23). The regression line along with the correlation coefficient (r) and its significance (p) is indicated. For both left ventricular ejection time and preejection period regression on plasma norepinephrine, the slopes are opposite for patients and control subjects (see Table V).

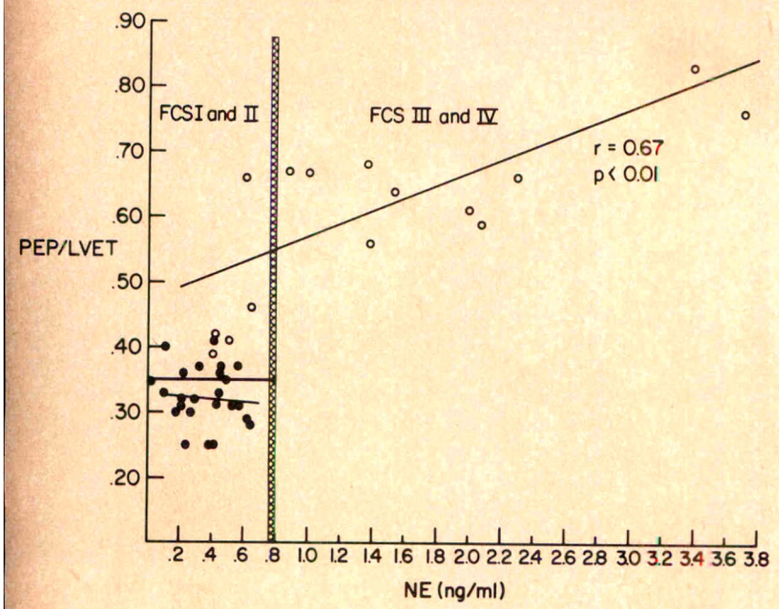

FIGURE 4. Regression of plasma norepinephrine concentration (NE) on the ratio of preejection period to left ventricular ejection time (PEP/LVET). Control subjects (**closed circles,** no. = 23) and patients (**closed circles,** no. = 16) with functional cardiac status (FCS) designations I and II are represented to the left of the **vertical cross-hatched line,** patients in functional classes III and IV to the right. The **solid horizontal line** (PEP/LVET = 0.35) represents the population mean for this laboratory. The regression line and correlation coefficient (r) for the patients with heart failure is indicated ($P < 0.01$).

failure.[26] However, Chidsey et al.[1] also reported that in patients with heart failure there was no statistically significant correlation between the magnitude of the urinary norepinephrine excretion and the severity of the heart failure although the excretion of norepinephrine tended to be greater in the most severely incapacitated patients. This difference between our findings and those of Chidsey et al.[1] appears to reflect the increased sensitivity of measuring plasma norepinephrine concentration with the enzymatic isotopic method of Henry et al.[19] as opposed to measuring urinary norepinephrine excretion. Plasma norepinephrine concentrations would appear to approximate more closely than urinary catecholamine excretion values the minute to minute changes of sympathetic neural activity, thus providing a more accurate tool for monitoring sympathetic activity.

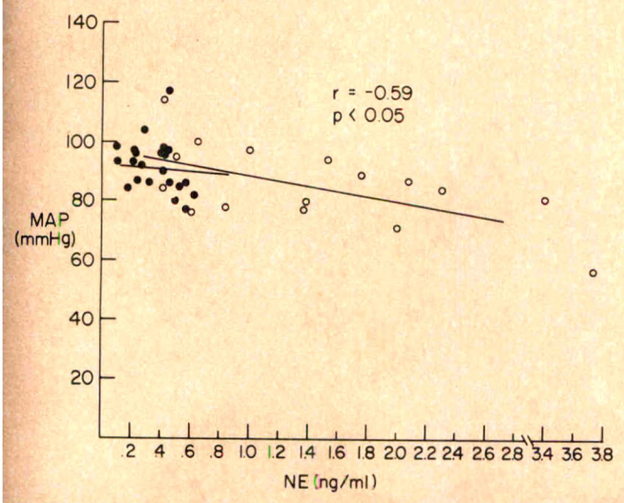

FIGURE 5. Relation between mean arterial pressure (MAP) and plasma norepinephrine concentration (NE). Control subjects are depicted by **closed circles** (no. = 23), patients with heart failure by **open circles** (no. = 16). The regression line and its correlation coefficient (r) are shown ($r = -0.59$, $P < 0.05$).

Plasma norepinephrine concentration and functional cardiac status: Our data demonstrate that the elevation of plasma norepinephrine levels correlates with the degree of clinical decompensation. This conclusion is based on the following observations: (1) patients in functional classes III and IV had significantly higher plasma norepinephrine concentrations on admission to this study than patients in functional class II; (2) patients with class II designations at the time of discharge from the study had significantly lower plasma levels of norepinephrine than patients in class III or IV; and (3) patients demonstrating either marginal or no change in their clinical condition also demonstrated minimal change in their plasma level of norepinephrine. However, these observations were true only for patients not receiving methyldopa. Patients receiving methyldopa had marked and significant reductions in their plasma norepinephrine concentrations that were disproportionately low considering their functional cardiac status. This suggests that methyldopa reduces adrenergic outflow from the central nervous system and peripherally in man and consequently reduces the circulating levels of catecholamines.

Correlation of plasma norepinephrine concentration, degree of heart failure and systolic time intervals: The observation that the elevated plasma norepinephrine concentration was indeed a reflection of the functional cardiac status of patients with heart failure was confirmed by the measurements of the systolic time intervals. Weissler et al.[23] have reported that congestive heart failure is characterized by a diminution of the left ventricular ejection time and a prolongation

of the preejection period but no change in the total electromechanical systolic interval (Q-S_2) when corrected for rate. These findings were confirmed in our study. In addition, these systolic intervals were shown to correlate very significantly with the plasma level of norepinephrine (Table IV). The most significant correlation with norepinephrine was that of the left ventricular ejection time, which reflects a progressive decrease in stroke volume in the presence of increasingly higher levels of plasma catecholamines in patients with congestive heart failure. The preejection period, which has been demonstrated to shorten in normal subjects after the intravenous administration of beta adrenergic receptor agonists,[27,28] was significantly prolonged (Fig. 3B) in patients with cardiac decompensation and correlated with high plasma levels of norepinephrine. This reflects a progressively slower velocity of isovolumic contraction in the patients with heart failure, in the presence of high plasma levels of norepinephrine.

In these patients, the opposite changes in the preejection period (PEP) and left ventricular ejection time (LVET) intervals as a function of the plasma norepinephrine level were clearly reflected in the PEP/LVET ratio, which increased as the plasma norepinephrine increased, demonstrating a highly significant correlation (Fig. 4). Because the PEP/LVET ratio has been shown by invasive studies to be well correlated with left ventricular ejection fraction and other measurements of left ventricular contractile performance,[29] the prolongation of the PEP/LVET ratio in the presence of increased plasma norepinephrine suggests an inverse relation between norepinephrine level and left ventricular ejection fraction. Ahmed et al.[30] demonstrated that either during exercise or after the intravenous administration of the beta receptor agonist (−) isoproterenol there is a significant decrease in the PEP/LVET ratio in normal subjects, due to a major decrease in the preejection period, with a smaller reduction in the left ventricular ejection time. Therefore, these patients with heart failure appear to respond in a manner opposite to that of normal subjects when the PEP/LVET is related to the level of catecholamine stimulation.

Our finding that patients with the most severe degree of left ventricular decompensation as shown by altered systolic time intervals demonstrated the highest levels of plasma norepinephrine suggests that, at best, the augmentation of sympathetic neural activity has failed to compensate adequately for a left ventricle exhibiting reduced ejection fraction and a marked decrease in stroke volume; at worst, it suggests that the high level of plasma norepinephrine actually contributes to the decrease in stroke volume and to the suppressed myocardial contractility by not exerting its expected biologic effect on the heart.

Beta receptor desensitization in patients with heart failure and elevated norepinephrine levels: The phenomenon of receptor desensitization has been described for the effects of polypeptide hormones such as insulin, vasopressin and luteinizing hormone, for neurotransmitters such as gamma amino butyric acid, and catecholamines.[31–35] For example, studies both clinical and experimental on insulin and its receptors have demonstrated that the concentration of insulin receptors is inversely related to the steady state concentration of the available insulin[36–39] and, from studies with isolated cell systems, it is clear that insulin can act directly to reduce the number of its own receptors.[40,41] In tissues as diverse as guinea pig tracheal muscle,[42] rat pineal gland[43] or frog erythrocyte,[44] it has been shown that beta adrenergic agonists are capable of producing beta receptor desensitization and that the degree of desensitization appears to be related to the potency of the agonist. The desensitization of the receptors was associated with a decrease in the total number of specific receptor binding sites as demonstrated by ^{3}H-l-alprenolol binding to beta receptors.

Because of reports such as these, it occurred to us that beta receptor desensitization might develop in patients with heart failure as a result of sustained elevated plasma norepinephrine levels. To examine this hypothesis, we tested the response to isoproterenol of lymphocytes from control subjects and patients with heart failure. The failure of lymphocytes from patients with advanced heart failure to generate normal amounts of cAMP may reflect a failure of beta receptor agonist isoproterenol to activate the membrane adenylate cyclase, and may be a demonstration of beta adrenergic receptor desensitization in these cells.

It is clear that an abundance of evidence exists to support the hypothesis that circulating hormones or pharmacologic agents both initiate the expected biologic response and act directly on cell receptors to cause a reduction in the number of available receptors and, thereby, a reduction of cell response. This evidence supports the proposal that the concentration of the specific receptors is inversely related to the maintained steady state concentration of the hormone or pharmacologic agent in the microenvironment surrounding the receptor.

Desensitization of cardiac beta receptors in chronic heart failure: We speculate that desensitization of cardiac beta receptors may be present in patients with chronic cardiac decompensation. The reasons for this speculation are summarized in the following evidence: (1) The heart rate and mean arterial pressure do not appear to respond appropriately to the large circulating norepinephrine concentration; (2) the preejection period is prolonged rather than shortened as would be expected if norepinephrine were exerting its inotropic effect; (3) the left ventricular ejection time is inappropriately shortened compared with its normal response to inotropic stimuli; (4) the PEP/LVET ratio, which normally decreases as a consequence of beta adrenergic receptor activation, shows a progressive increase with increasingly higher levels of plasma norepinephrine; and (5) peripheral blood lymphocytes from patients with the highest plasma levels of norepinephrine and the greatest degree of cardiac decompensation failed to generate a normal amount of cAMP after stimulation with the beta adrenergic receptor agonist. If desensitization exists in these patients, it is probably related to the maintained high levels of plasma nor-

epinephrine we have observed. The importance of this presumed desensitization is two-fold. First, it deprives the heart of one of its major inotropic processes in the presence of a diseased myocardium with altered contractility; second, it reverses the effectiveness of sympathetic activation when exercise-induced increases in the circulatory demand occur.

Clinical implications: That the phenomenon of desensitization might be operative in patients with severe congestive failure is supported by two recent reports encompassing both clinical and experimental research in heart failure. Waagstein et al.[45] reported that chronic beta adrenergic receptor blockade with the beta antagonists (−) alprenolol and (−) practolol for periods up to 1 year in patients with congestive cardiomyopathy refractory to conventional methods of therapy resulted in improvement in their clinical condition, with a decrease in exertional dyspnea and an increase in physical exercise tolerance. Noninvasive cardiologic measurements demonstrated an increase in the left ventricular ejection time in these patients with beta blockade, indicative of an increase in stroke volume. This could have resulted from a restoration of receptor sensitivity due to prolonged beta blockade. Newman[46] studied the inotropic response of the left ventricle to the intravenous administration of graded doses of norepinephrine and isoproterenol in dogs with congestive heart failure. Cardiac contractile responses to norepinephrine and isoproterenol were significantly depressed in dogs with heart failure when compared with control dogs. Both of these studies suggest that once decompensation occurs, norepinephrine appears not to produce the expected inotropic effect and may in fact increase the functional deficit. It is significant that Waagstein et al.[45] believed that blockade of beta adrenergic receptors of the myocardium was essential for favorable treatment in their patients with congestive cardiomyopathy, by demonstrating that cessation of treatment with the beta blocking agents rapidly resulted in decompensation.

In summary, our results clearly demonstrate that the plasma level of norepinephrine is directly related to the degree of left ventricular dysfunction both by clinical observation and by noninvasive cardiologic measurements in patients with cardiac failure. In addition, lymphocytes from patients with heart failure fail to generate normal amounts of cyclic 3′,5′-adenosine-monophosphate upon exposure to isoproterenol. We suggest, therefore, that beta adrenergic receptors are desensitized in these patients and that this contributes to the observed alterations in contractility.

Acknowledgments

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Electrophysiologic Studies on Atrioventricular Nodal Wenckebach Cycles

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Wenckebach cycles with a 4:3 ratio, produced by rapid atrial pacing, were studied in 27 anesthetized denervated dogs using programmed stimulation. A test stimulus (S′) could be inserted after any preselected beat of the Wenckebach cycle. An on-line computer measured the atrial (A) to His bundle (H) intervals. In all dogs a progressive increase in atrioventricular (A-V) nodal refractoriness was seen in the effective refractory period for each beat and a rightward shift of the A′-H′ relative to the A-A′ refractory curves. Atypical Wenckebach cycles could be produced by small changes in the basic cycle length. No evidence for reentry was found from the refractory curves of Wenckebach cycles and by interruption of stimulation after the third stimulus of a 4:3 Wenckebach cycle. Analysis of the A′-H′ relative to the H-A′ refractory curves did not confirm a positive feedback mechanism. In order to mimic a Wenckebach cycle, a blocked premature beat was inserted during stressed 1:1 conduction. The changes in the refractory curves for successive beats after the premature beat were rate-dependent and similar to those in Wenckebach cycles but smaller in magnitude. In Wenckebach cycles there is a progressive increase in refractoriness, caused by cumulative effect similar to that seen after a blocked beat during stressed 1:1 conduction, until block occurs and the cycle resets.

Although atrioventricular (A-V) nodal Wenckenbach block was described three quarters of a century ago[1] and is important to the understanding of A-V conduction disorders, it remains imperfectly defined and understood. A large incidence of atypical cycles is recognized,[2,3] and various phenomena have been evoked to explain the arrhythmia. These include decremental conduction,[4] summation,[5] inhomogeneous conduction,[6,7] electrotonus and temporal shifts in the recovery of A-V nodal cells,[8] dual conduction pathways,[3] reentry[9,10] and a positive feedback effect.[11,12]

To date, there have been few reported studies on Wenckebach cycles using a programmed stimulation technique despite the contribution of this technique to the understanding of various other arrhythmias.[13] The present investigation was undertaken using a programmed stimulation technique for the following purposes: (1) to define by refractory curves the functional properties of the A-V node for each beat during the Wenckebach cycle, (2) to study the effect of changes in basic cycle length on the refractory curves and the resultant Wenckebach cycles, (3) to assay for reentry during the cycle, (4) to evaluate the possibility of a positive feedback mechanism, (5) to define a fatigue or cumulative effect after a blocked beat during 1:1 conduction, and (6) to explore the role of a cumulative effect in the production and maintenance of Wenckebach cycles.

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Methods

Animal preparation: Experiments were performed in 27 adult mongrel dogs of either sex weighing 10 to 15 kg and anesthetized with sodium pentobarbital (30 mg/kg intravenously). The chest was opened using a right thoracotomy and the dog ventilated by a positive pressure respirator at a minute-volume determined from a body weight nomogram. Body temperature was maintained with a pediatric heating blanket. Normal saline solution was administered throughout the experiment (10 ml/kg per hour). In preliminary experiments the Wenckebach periodicity proved unstable unless the heart was denervated. Consequently, in all experiments the cervical vagi were cut and the stellate ganglia removed. Close bipolar plunge electrodes[14] were used to record simultaneously from the low right atrial septum, the His bundle and the low left ventricular septum at the site of earliest ventricular activation. The electrode amplifiers (Bloom Associates, Ltd., Narberth, Pennsylvania) had a 40 to 500 hertz bandpass and a noise level of less than 5 microvolts. A lead II electrocardiogram was continuously monitored. Plunge electrodes were applied to the right atrial appendage to pace the hearts; the stimulus was 4 msec long and two times the voltage threshold.

Stimulation instrumentation: The basic format of the experiments was to induce Wenckebach periodicity by rapid atrial pacing and then to insert a test stimulus after each beat of the Wenckebach cycle. To perform the experiment efficiently, we developed a stimulator that could insert a test beat after any preselected beat in the Wenckebach cycle.

The stimulator worked in the following manner: An amplified ventricular electrogram was detected by comparator which had a 120 msec lockout feature so that only one pulse per beat was generated. These pulses drove a missing pulse detector that allowed the blocked beats to be detected; an output was produced when the time between the input pulses exceeded a preselected interval. The output from the missing pulse detector reset a counter that was clocked by the stimulator driving the heart; thus, the stimuli after a blocked beat were counted. When a preselected count was reached, the driving stimulator was interrupted, an external digital stimulator (Bloom Associates) was enabled and it inserted a test stimulus after a preselected variable test interval. After the test stimulus, the basic driving stimulation was immediately resumed. The basic driving stimulator was a continuously variable analog unit with a precision of ±25 μsec and a resolution of 100 μsec; the test stimulus generator had a precision of ±50 μsec and a resolution of 1 msec.

The stimulation system could therefore synchronize onto the Wenckebach cycle, count the beats after a blocked beat and reliably insert a test beat after any preselected beat of the Wenckebach cycle. Using this instrument, we could repeatedly scan through the Wenckebach cycle with a given test interval, first inserting the test beat as the first beat of the cycle, then as the second beat, and so on.

Data acquisition and processing: In pilot experiments it was found that the time necessary to analyze the data using manual and analog techniques was prohibitive, and it was difficult to achieve adequate resolution. Consequently, we developed electronic instrumentation that detected, timed and statistically analyzed the electrophysiologic signals on line while the experiment was proceeding.

The instrumentation operated as follows: The signal from the low atrial septum (A), derived either from the His bundle electrogram or from a separate plunge electrode, was detected with a comparator circuit that was adjustable for level and slope. The output from the comparator passed through a gate that opened at an adjustable time after the stimulus (usually 20 msec) and closed after a variable interval, set to be shorter than the earliest detected His signal. The first signal from the atrial comparator that passed through the gate was interpreted as the atrial timing signal. The His bundle electrogram (H) was similarly processed except that the His gate opened after the atrial gate had closed and was kept open until 15 msec after the next stimulus in order to detect long A-H intervals. The atrial and His bundle timing signal controlled a Hewlett-Packard 5326A timer that continuously measured the A-H and the H-A intervals; the time resolution was set at either 10 or 100 μsec. If baseline drift or large local T waves interfered with detection of either the atrial or bundle of His signals, then 2 pole 30 hertz active filters were inserted before both the His bundle and the atrial comparators. The comparators were usually set to detect the largest and most rapidly moving component of the electrogram. Although this was not necessarily the earliest component in the electrogram, it was determined to have the most time stability. All electrograms and the status of the gates were continuously monitored on an eight channel storage oscilloscope (Tektronix 5103).

The data from the interval counter were stored in a temporary memory bank and joined there with coding information from the logic circuitry containing the following information: the status of the gates, whether or not a signal was detected when the gates were open, whether the stimulus was a basic driving or a test stimulus and the number of the beat in the Wenckebach cycle. The contents of the temporary memory were entered into a programmable calculator (Hewlett-Packard 9820A) that decoded the information, performed statistical analysis and printed the data in an easily readable format. The entire system functioned to detect the electrograms, measure their intervals and then present the data to the experimenters in real time.

The analog data and the signals from the electronic logic were recorded on magnetic tape using a Honeywell 5600C frequency modulation tape recorder. These data were later recorded on 35 mm film at a film speed of 200 mm/sec and projected onto a Hewlett-Packard 9864A digitizer board. To verify the electronic data analysis system, appropriate samples of the data were analyzed using the digitizer board and calculator. The resolution of this system was less than 0.5 msec.

Except for the commercially available equipment, the instrumentation used in this study was engineered by one of us (MBS) using standard linear and digital circuits.[15]

Experimental protocol: Before the experiments began, the measuring system was used to study the electrophysiologic stability of the animals and the stability of the electrographic configurations by evaluating the reproducibility of A-H conduction intervals during atrial pacing at a basic cycle length of 350 to 450 msec. Changes in the electrograms were the major source of variability in conduction intervals. Electrodes were readjusted until unambiguous and stable signals were obtained and a standard deviation of less than 1 percent was achieved for 20 consecutive A-H intervals. The mean standard deviation for all dogs was 0.6 percent. Stability of the electrograms during premature beats was studied by recording on the storage oscilloscope.

During studies on the Wenckebach periodicity, a test atrial response (A′) was evoked at different times both before and after the normally expected atrial response in order to scan conduction times and refractoriness of each beat in the cycle. Refractory curves were recorded by inserting the same test interval after each beat in the cycle. With each test interval and at each location within the Wenckebach cycle, six A′-H′ intervals were recorded. At least four control Wenckebach cycles were allowed between each test interval. Each beat of

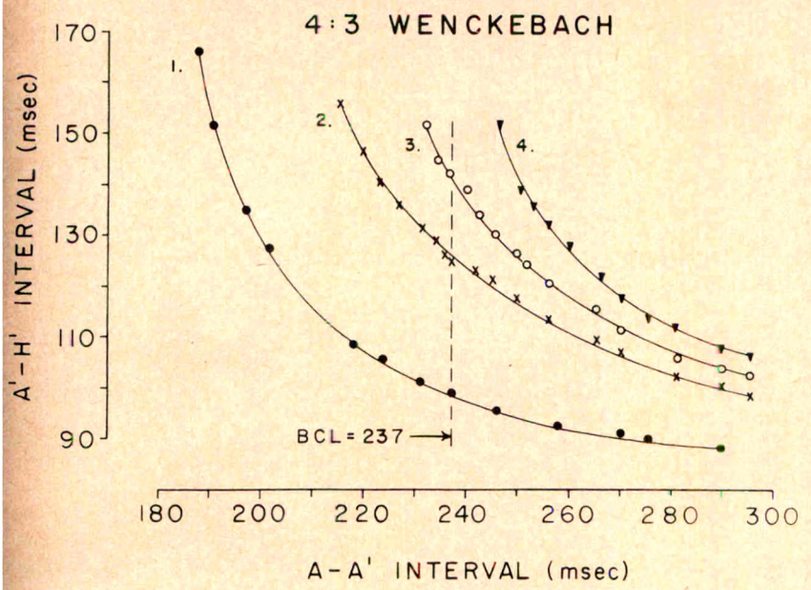

FIGURE 1. Refractory curves during 4:3 Wenckebach cycles. On the **vertical axis** is the A-V nodal conduction time for the test stimulus (A′-H′ interval). On the **horizontal axis** is the atrial test interval (A-A′), the time between the low atrial septal depolarization arising from the last basic cycle length stimulation to the atrial depolarization caused by the test stimulus. The basic cycle length (BCL) was 237.3 msec. Each point represents the mean of six observations. The control A-H conduction times were 100.9 ± 0.3 msec for the first beat, 126.4 ± 0.4 msec for the second beat and 143.7 ± 0.8 msec for the third beat. See text for details.

the Wenckebach cycle was tested with the same test interval before another test interval was used; approximately 2 minutes were required to record six intervals for all four beats of a 4:3 Wenckebach cycle. The test interval was then incremented to 5 to 20 msec and another cycle of testing initiated.

The effective refractory period, defined as the shortest atrial test interval that was reliably conducted, was determined to the nearest millisecond. The testing began at a test interval that was shorter than the effective refractory period after the first conducted beat of the Wenckebach cycle.

The conduction times of control 4:3 Wenckebach cycles were recorded frequently throughout testing. If the conduction times of the cycles had drifted from the control values, then a small readjustment of the basic cycle length was made. However, no adjustment of the basic cycle length was allowed while testing in the interval extending from the effective refractory period after the first conducted beat until 30 msec after the effective refractory period after the third beat. If at any time in testing during that interval the conduction times of the Wenckebach cycles had drifted from control values, the entire run was aborted and a new run begun. It was found that the basic cycle length could be readjusted when one was further than 30 msec beyond the effective refractory period of the third beat, since by that time the refractory curves were flat and relatively insensitive to small changes (less than 5 msec) in the basic cycle length. After each injection of pentobarbital anesthesia, the basic cycle length necessary to maintain 4:3 cycles lengthened transiently. However, after 10 to 15 minutes the same basic cycle length returned. No testing was done immediately after each injection of pentobarbital. Refractory curves were determined during Wenckebach cycles in all dogs in which this experiment was attempted.

Statistical methods: Statistical comparison of conduction times of different beats for the same test interval was made with use of Student's t test. Effective refractory periods were compared using the Fischer exact test comparing the number of test beats conducted in one location of the Wenckebach cycle with the number of test beats conducted for the same test interval at another location in the cycle. Listed results are means ± standard deviations.

Results

Rapid atrial pacing induced stable second degree A-V nodal block of a 4:3 Wenckebach periodicity in all 23 dogs in which it was attempted. Each dog produced classic[2,3,16,17] Wenckebach cycles; the A-H conduction time progressively increased for beats 1 through 3 and the largest increase in conduction time occurred between the first and second beats. The mean basic cycle length was 251.2 ± 32.4 msec (mean ± standard deviation). The A-H conduction time was 107.8 ± 20.1 msec for the first beat, 142.8 ± 23.7 msec for the second beat and 162.4 ± 29.0 msec for the third beat.

Stable 4:3 Wenckebach periodicity could easily be induced over a narrow range of basic cycle lengths; the range was usually 4 to 8 msec wide. Wenckebach cycles with a ratio higher than 4:3 were found to be unstable. In our denervated canine heart model 4:3 Wenckebach cycles were stable for several hours with only small adjustments (10 to 20 msec) in the basic cycle length. The conduction time for each beat of the cycle was quite precise. For each dog 10 to 20 consecutive cycles were analyzed, and the average standard deviation of the A-H conduction time, expressed as percent, was 0.7 percent for the first beat, 0.8 percent for the second beat and 1.3 percent for the third beat.

Refractory Curves for Wenckebach Cycles

Refractory curves were determined during Wenckebach periodicity using stimulator that could insert a test stimulus after any preselected beat of the Wenckebach cycle. The test beat was inserted multiple times in each location of the cycle; all four beats of the cycle were scanned with the same test interval before the next test interval was used.

Figure 1 records the results of such testing in a typical experiment. When the test stimulus was inserted at the first beat of the Wenckebach cycle, that is, just after the blocked beat of the preceding cycle, curve 1 was generated. Curves 2, 3 and 4 were produced when the test beat stimulus was in-

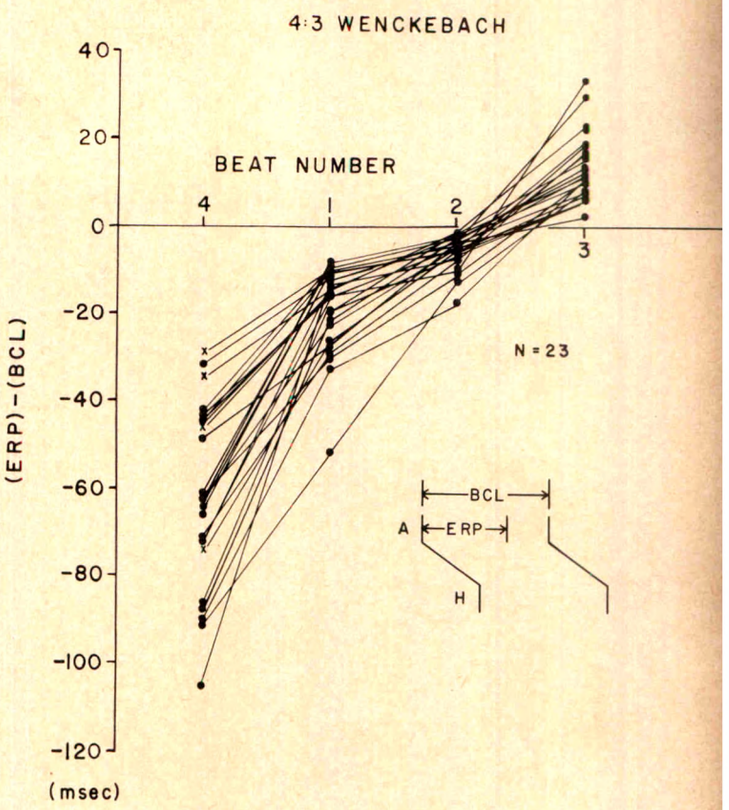

FIGURE 2. The relation between the effective refractory period (ERP) and the basic cycle length (BCL) for each beat of 4:3 Wenckebach cycles in 23 dogs. On the **horizontal axis** is the beat number. On the **vertical axis** is the difference between the effective refractory period after a given beat and the basic cycle length. The four points marked with a **cross** represent experiments in which the atrial functional refractory period was longer than the A-V nodal effect refractory period after the blocked beat. The effective refractory period was determined to the nearest millisecond. The effective refractory period after beat 4, the blocked beat, was 184 ± 23 msec, 66 ± 23 msec shorter than the basic cycle length; after the first beat it was 233 ± 30 msec, 19 ± 12 msec shorter than the basic cycle length; after the second beat it was 245 ± 31 msec, 6 ± 5 msec shorter than the basic cycle length; after the third beat it was 264 ± 34 msec, which exceeded the basic cycle length by 12 ± 7 msec. N = number of dogs.

serted as the second, third or fourth beat in the Wenckebach cycle. The A-V nodal effective refractory period is defined as the shortest atrial test interval that was reliably conducted. The effective refractory period after a given beat is denoted by the point on the curve for the next beat that has the minimal A-A′ interval. Earlier test beats were blocked. Figure 1 illustrates that as the Wenckebach cycle advances, there is a progressive increase in the refractoriness of the A-V node as marked by an increase in conduction time and an increase in the effective refractory period. The conduction time increases from beats 1 through 4 for any given test interval shown in ($P < 0.001$). The effective refractory period after the blocked beat, the fourth beat, is shorter than any subsequent effective refractory period; this period is marked by the point on curve 1 that has the minimal A-A′ interval (187 msec). The effective refractory period after the first beat (214 msec) is longer and the effective refractory period after the second beat is longer still (233 msec). The effective refractory period after the third beat (246 msec) exceeds the basic cycle length and consequently the fourth beat does normally not conduct. The fourth beat would conduct if the test interval were longer than the basic cycle length and effective refractory period after the third beat. Refractory curves during Wenckebach cycles were recorded in 23 dogs; they were all qualitatively similar to those in Figure 1.

Figure 2 illustrates the relation between the effective refractory period and the basic cycle length for each beat of 4:3 Wenckebach cycles in 23 dogs. In 4 of the 23 dogs, the atrial functional refractory period was longer than the effective refractory period of the A-V node after the blocked beat; in these cases (marked with an X in Fig. 2) the A-V nodal effective refractory period is only approximated. In all dogs there was a progressive increase in the effective refractory period as the Wenckebach cycle proceeded. Excluding the four experiments in which the effective refractory period after the fourth beat could not be reliably determined, the following mean results were obtained: The effective refractory period after beat 4, the blocked beat, was 184 msec. After the first beat, the effective refractory period was longer, 233 msec; after the second beat, it was further lengthened to 245 msec, which was only 6 msec shorter than the basic cycle length. After the third beat, the effective refractory period was 264 msec, which exceeded the basic cycle length by 12 msec. The effective refractory period after the third beat in all dogs was longer than the basic cycle length, hence the next beat, the fourth beat, was blocked.

The increase in effective refractory period as the Wenckebach cycle proceeded was highly variable. The largest increase in the effective refractory period occurred after the first conducted beat; among the 19 dogs in which the effective refractory period after the blocked beat could be determined, 18 showed the largest increase in the effective refractory period between beats 4 and 1. Although all dogs showed typical[2,3,16,17] Wenckebach progression in conduction times as the cycle proceeded, the effective refractory period did not increase with decreasing increments in 13 of the 23 dogs. In those dogs, the increase in the effective refractory period from beat 1 to beat 2 was smaller than the increase from beat 2 to beat 3. For each dog the increase in effective refractory period from beat 4 to beat 1, from 1 to 2, and then from 2 to 3 was significant ($P < 0.001$).

Effects of Changes in Basic Cycle Length

It is apparent from examining Figures 1 and 2 that during the Wenckebach cycle the A-V node is operating at four dis-

tinct states of refractoriness as defined by the four different refractory curves. The conduction times observed during the control cycles represent intersection of the basic cycle length with the refractory curves. It was found that small changes in the basic cycle length do not markedly alter the refractory curves during the Wenckebach cycle but could produce relatively large changes in the conduction times of the cycle. This was especially true for the last conducted beat, beat 3, because the basic cycle length intercepts refractory curve for that beat at a relatively steep portion of its curve.

Figure 3 illustrates the relation between small changes in basic cycle length and the resulting conduction times during a 4:3 Wenckebach cycle. The refractory curves were recorded at a basic cycle length of 275 msec. The control conduction times represent the intersections of the refractory curves with a vertical line representing the control basic cycle length of 275 msec. When the basic cycle length was shortened to 270 msec or lengthened to 277 msec, 4:3 Wenckebach cycles with different conduction times were recorded (illustrated by two sets of open circles). It is clear that the points recorded at the basic cycle lengths of 270 and 277 msec fall along the same refractory curves that were recorded at the control cycle length; the different basic cycle lengths intersect the same refractory curves at slightly different points. The conduction times for the 3 different basic cycle lengths are illustrated in Table I.

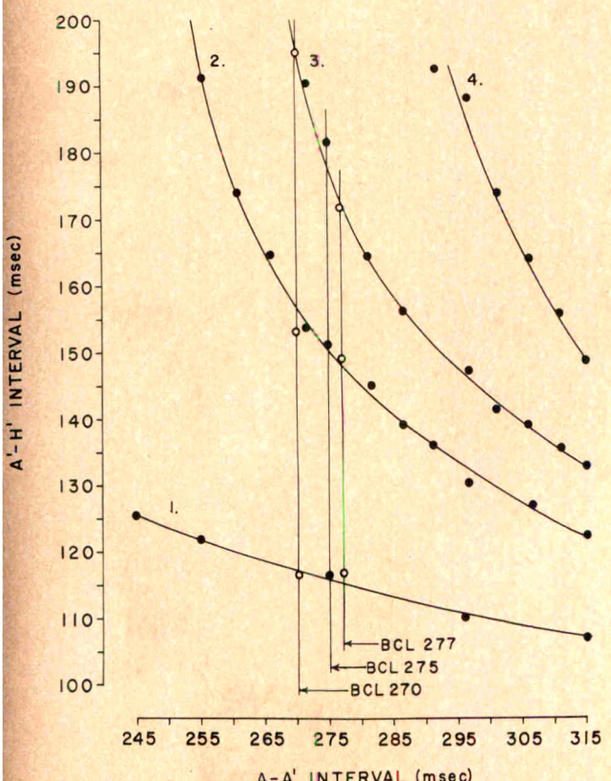

FIGURE 3. The A-V nodal conduction time (A′-H′) for a test beat versus the test interval (A-A′) for each beat of a 4:3 Wenckebach cycle at a basic cycle length (BCL) of 275 msec. The **open circles** are the control conduction times recorded when the basic cycle length was changed to 270 and 277 msec. Each point represents the mean of 6 to 10 observations.

TABLE I

A′-H′ Conduction Time for the 4:3 Wenckebach Cycles at Three Different Basic Cycle Lengths

Beat no.	Basic Cycle Length (msec) 277.0		275.0		270.1
1	115.9 ± 0.6		115.3 ± 1.2		115.5 ± 1.0
2	147.6 ± 1.5	*	150.2 ± 1.2	*	152.8 ± 2.3
3	170.9 ± 6.1	*	180.7 ± 8.3	*	194.6 ± 10.7

* $P < 0.01$.

The experiment is the same as that depicted in Figure 3. The values in msec are means ± standard deviation.

In the area of interest, the refractory curve for beat 3 has a steep slope (−3.4) and, consequently, the conduction times for the last conducted beat, the third beat, differ markedly (Table I). Expressed as percent change, an increase in the basic cycle length of 2.5 percent (270 to 277 msec) caused a decrease of 14 percent in the conduction time of the third beat (195 to 171 msec). At the longer cycle lengths of 275 and 277 msec, the Wenckebach cycle shows typical progression in conduction times; for example, at a cycle length of 275 msec, the increment in conduction from beat 1 to 2 (34.9 msec) is greater than from beat 2 to 3 (30.5 msec). At a cycle length of 270 msec, however, the Wenckebach cycle becomes atypical, and the increment in conduction time for beat 1 to 2 (37.3 msec) is less than the increment from beat 2 to 3 (41.8 msec).

During 4:3 Wenckebach periodicity, the A-V node functions at four distinct levels of refractoriness, as denoted by the refractory curves, and, at the time of the last conducted beat, the A-V node is very close to its effective refractory period and sensitive to the exact timing of atrial stimulation. Small changes in the basic cycle length can have large changes in the conduction times observed during Wenckebach cycles and can convert a cycle from one having a typical progression in conduction time to one that has an atypical progression. It is apparent from Figures 1 and 3 that 4:3 Wenckebach periodicity could be produced over a small range of basic cycle lengths. With further shortening of the basic cycle length, it would be expected that ultimately the third beat of the cycle would be blocked, when the basic cycle length became less than the effective refractory period after the second beat. Shortening of the cycle length would convert the 4:3 cycle into a 3:2 cycle.

To study the relation between cycle length and refractoriness of the A-V node during Wenckebach cycles of varying ratios, we drew refractory curves during 4:3, 3:2 and 2:1 cycles in three dogs (Fig. 4). At a basic cycle length of 261 msec, 4:3 Wenckebach periodicity was recorded (panel A). The refractory curves drawn during this rhythm were similar to those previously discussed. When the basic cycle lengths were shortened to 251 msec, a 3:2 Wenckebach cycle resulted (panel B); the third stimulus occurs during the effective refractory period after the second beat and the third beat does not conduct. If the third beat were delayed by 9 msec or longer, then it would conduct. With further shortening of the basic cycle length, 2:1 A-V nodal block was produced (panel C). It is apparent from the refractory curves drawn during this rhythm that the basic underlying phenomenon is the same as during 4:3 and 3:2 Wenckebach cycles. The basic cycle length of 230 msec is less than the effective refractory period after the first beat and the second beat fails to conduct. When the stimulus was delayed by 20 msec or longer, however, the second beat began to conduct.

The conversion from a 4:3 cycle to a 3:2 and then to a 2:1

cycle, which occurs because of shortening of the basic cycle length, is aided by a frequency-dependent increase in the refractoriness of the A-V node. In general, as the basic cycle length shortened, all the refractory curves shift rightward, denoting increasing refractoriness. For example, at a cycle length of 261 msec, the effective refractory period after the second beat is 254 msec (Fig. 4A). At a cycle length of 251 msec, after it increases to 260 msec (Fig. 4B). At the same time that the basic cycle length shortened, the refractory curve for the third beat moves rightward. Similarly, as the basic cycle length is shortened from 261 msec (4:3 cycle) to 230 msec (2:1 cycle), the effective refractory period after the blocked beat lengthens (174 to 205 msec), as does the effective refractory period after the first beat (245 to 250 msec).

Although the increase in refractoriness could be due to the change in conduction ratios of the Wenckebach cycles, data recorded during 1:1 conduction, to be discussed later, suggest that it is a rate-dependent effect. The increase in refractoriness resulting from a decrease in cycle length implies that, from the refractory curves recorded during 4:3 Wenckebach

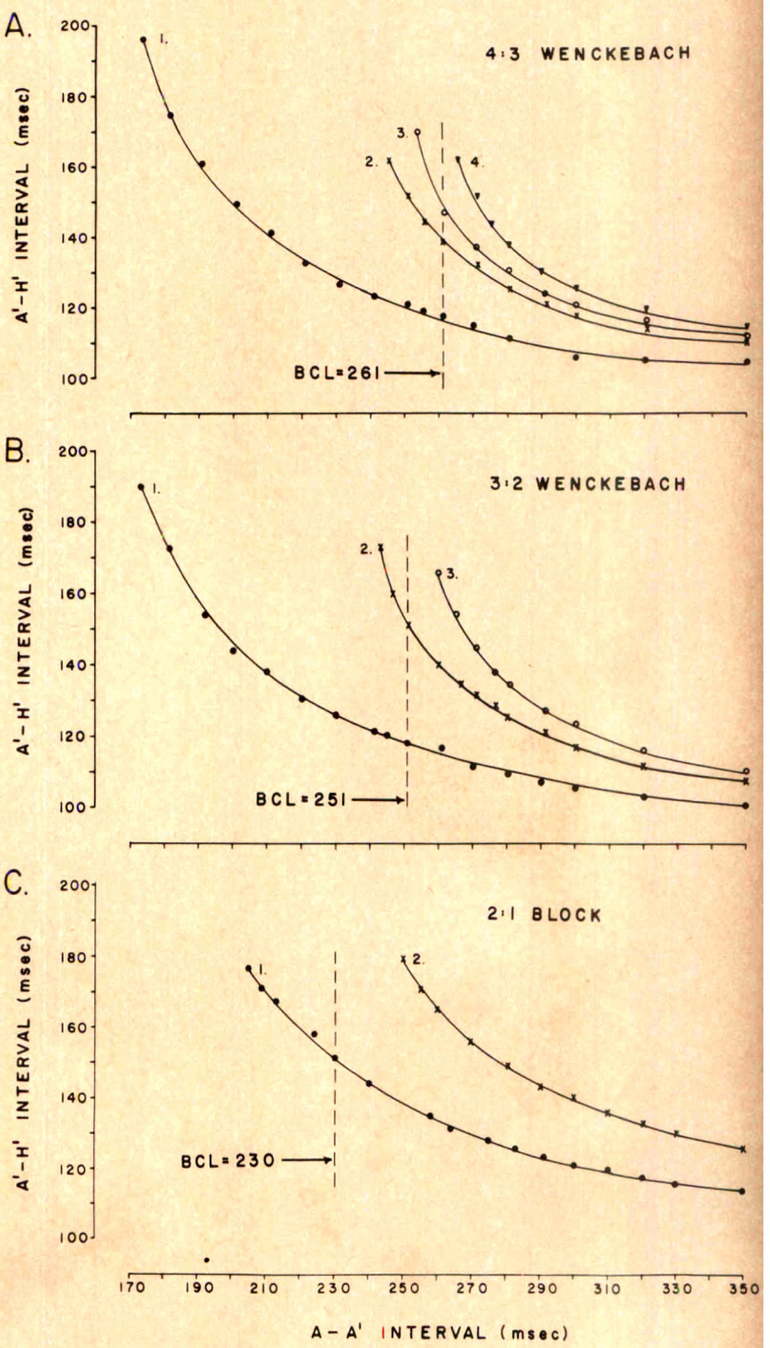

FIGURE 4. The conduction time (A′-H′) for a test beat versus the test interval (A-A′) for each beat of Wenckebach cycles recorded at three different basic cycle lengths (BCL) in the same dog (216 msec in A, 251 msec in B and 230 msec in C). Each point represents the mean of six observations.

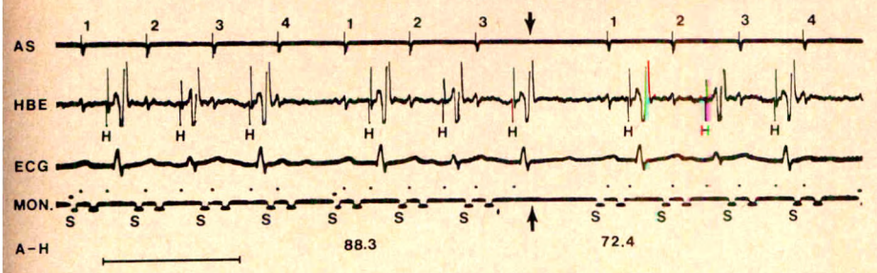

FIGURE 5. No reentry during 4:3 anterograde Wenckebach cycles. Tracings from above downward are a recording from the low atrial septum (AS), the His bundle electrogram (HBE) (His depolarizations are marked with an H), a lead II electrocardiogram (ECG) and a monitor signal (MON.) that depicts the activity of the atrial and His detection circuits; the transitions marked with an S occurred at the time of the stimulus. A control 4:3 Wenckebach cycle is shown. After the third beat of the second cycle, the stimulus was interrupted **(arrows).** No atrial echo was seen after the third beat. The basic cycle length was 234.3 msec. The A-H intervals for beats 1 to 3 were 88.3 ± 0.9 msec, 118.5 ± 1.5 msec and 128.0 ± 2.1 msec. The time calibration is 500 msec.

periodicity, one could not predict precisely the refractory curves during the shorter cycles. In other words, the refractory curves for a 4:3 Wenckebach rhythm were not superimposable with the refractory curves from the 3:2 and 2:1 rhythms.

Reentry During Wenckebach Cycles

It has been suggested that reentry occurs continuously during Wenckebach cycles and that the last beat of the cycles is blocked because of a collision and cancellation between a reentrant beat and the normally conducted beat.[9,10] Experimental results supporting this hypothesis have been obtained in Wenckebach cycles produced by retrograde stimulation of the A-V node in dogs and during anterograde and retrograde stimulation in the human and rabbit heart.[6,7,9,10,18–20]

In our experiments reentry did not occur during Wenckebach cycles. There are three lines of evidence supporting this conclusion: First, the refractory curves recorded during 4:3 anterograde Wenckebach cycles demonstrate that the blocked beat will conduct if the stimulus is delayed by a small interval, a mean of 12 msec for all 23 dogs (Fig. 2). If a reentrant beat were arising from the last conducted beat, the third beat, then a delay of the stimulus at the time of the fourth beat would allow the reentrant beat to proceed through the node even farther and eventually emerge in a retrograde direction. The effect of the emerging reentrant beat would be to leave the A-V node considerably more refractory than after a normally conducted beat. One would therefore expect that the effective refractory period after the third beat would be considerably prolonged. The fact that the fourth beat would conduct if the stimulus were delayed a mean of 12 msec implies that the A-V node was not engaged by a reentrant beat conducting in a retrograde fashion.

In 16 dogs further experiments were performed to test directly for reentry during 4:3 Wenckebach cycles. In these experiments, stimulation was interrupted after the stimulus producing a third beat to assay for a reentrant beat; if reentry were occurring during Wenckebach cycles, one would expect an atrial echo after the third beat.[9,10] Figure 5 illustrates a typical experiment. Stable 4:3 Wenckebach cycles were produced by rapid atrial pacing at a basic cycle length of 234.3 msec. After four control cycles, atrial stimulation was interrupted after the stimulus producing the third beat (arrows). As can be seen, there is no evidence of an atrial or ventricular echo occurring after the third beat of the cycle. Stimulation was interrupted for a period of time equal to two times the basic cycle length. Assuming that retrograde conduction began as late as the last His potential of the cycle, 340 msec was allowed for the reentrant beat to emerge, a period 2.7 times longer than the longest anterograde conduction time in the cycle. The first atrial response after the pause in stimulation was paced, and the latency was unchanged. This experiment was performed 588 times in 16 dogs. No examples of atrial or ventricular echoes were seen during any of these trials.

Another line of evidence against reentry during anterograde 4:3 Wenckebach cycles is that, when the fourth stimulus was not delivered, the first beat of the next cycle always had a shorter conduction time. In Figure 5, for example, the control conduction time for the first beat is 88.3 msec. After the cycle in which the stimulation was interrupted, the conduction time for the first beat of the next cycle was shorter, 72.4 msec ($P < 0.001$), and similar to the conduction time (69.5 msec) recorded in the same dog during 1:1 conduction at a cycle length of 450 msec. This phenomenon was seen in all 16 dogs in which the experiment was performed. The conduction time was shortened by a mean of 15.3 ± 7.1 msec. The decrease of the conduction time implies that during 4:3 Wenckebach cycles concealed conduction occurs;[21–25] the fourth stimulus penetrates into the A-V node, is blocked there and prolongs the refractoriness of the A-V node. When the fourth stimulus is not delivered, then the A-V node is less refractory and can conduct more rapidly. If there were reentry after the third beat of the cycle, and if the reentrant beat were blocked in its retrograde passage through the node, one would expect that it would leave the node refractory to a degree similar or greater than that after the blocked fourth beat in a normal cycle.

Wenckebach Phenomenon as a Manifestation of Positive Feedback

Levy et al.[11,12] hypothesized that the Wenckebach phenomenon can be described in terms of a positive feedback mechanism. In this theory, the conduction time of a test beat (the P′-R′ interval in their experiments) is expressed as a function of the preceding R-P′ interval, that is, P′-R′ = f(R-P′). Because the P-P′ interval by definition equals P-R + R-P′, one could predict subsequent P′-R′ intervals on the basis of knowing one P-R interval if one knew the P-P′ intervals and if the function P′-R′ = f(R-P′) were stable. Depending on the exact shape of the curve that defines the function and depending on the P-P′ intervals, a series of P′-R′ conduction times could show a variety of behavior such as convergence to a final value, or a gradual increase and eventual block, as during Wenckebach periodicity. Levy and coworkers[11,12,26] have provided and analyzed examples of such behavior. On the basis of conduction studies in the rat heart, Van Capelle et al.[27] suggested a mechanism for Wenckebach cycles similar to positive feedback.

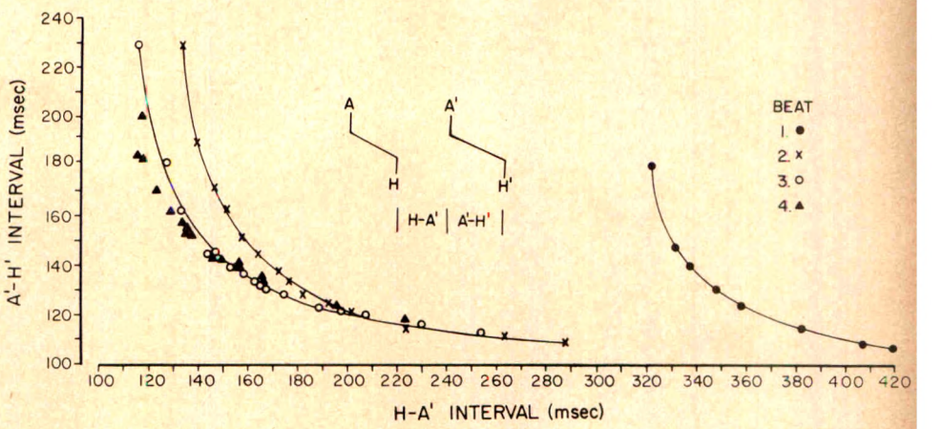

FIGURE 6. The conduction time for a test beat (A′-H′) versus the interval from the preceding His bundle signal to the low atrial septal electrogram for the test beat (H-A′). All four beats of a 4:3 Wenckebach cycle were tested. The symbol identification for the four beats is shown. The basic cycle length was 275.0 msec. The refractory curves in this figure were recorded simultaneously with the refractory curves shown in Figure 3 in the same experiment. Each point represents the mean of six observations.

For the positive feedback theory to be useful as a description of A-V nodal function, one must be able to define a function P′-R′ = f(R-P′) that is stable or at least varies predictably over time and with different perturbations. If the function varied unpredictably after a perturbation such as a blocked beat, then one could not use it to predict subsequent P-R intervals. The mathematical model would have limited value because one could not use it to define conduction time under varying circumstances. In our experiments on Wenckebach periodicity, the A-V node caused the varying A-V conduction times; in other words, the atrial and infranodal conduction times did not vary significantly (less than 0.5 msec) during the Wenckebach cycles, as previous workers have noted.[18,28,29] One could therefore convert the equation P′-R′ = f(R-P′) into the equivalent form A′-H′ = f(H-A′) by subtracting the constant atrial and infranodal conduction times.

We tested for a positive feedback mechanism during Wenckebach cycles in 23 dogs by assaying the stability of the function A′-H′ = f(H-A′) for each of the four beats during a 4:3 cycle. The function was defined by plotting the refractory curves expressing the A′-H′ interval as a function of the H-A′ interval for each of the four beats during testing with programmed stimulation. Figure 6 records a typical example. As can be seen, the relation between the A′-H′ and H-A′ intervals, is not constant throughout the Wenckebach cycle. The curve for the first beat is shifted rightward from the curves of subsequent beats because, to measure the H-A′ interval for the first beat, one must go back to the His potential of the last conducted beat, the third beat. The curves for the second through fourth beats, however, do not lie along the same curve; instead, there is a family of at least two and perhaps three separate curves that define the function A′-H′ = f(H-A′) during those beats. By comparing the H-A′ interval at the same A′-H′ interval for different beats, at least three statistically distinct curves were found in all 23 dogs. In Figure 6 the curves for beats 1, 2 and 3 were distinct from each other ($P < 0.001$) over the A′-H′ interval of 130 to 230 msec. Moreover, expressing the A′-H′ conduction time as a function of the H-A′ interval appears no more precise than expressing it as a function of the A-A′ interval. Figures 3 and 6 were recorded simultaneously from the same dog. In both figures, the refractory curves for the second and third beats are separated horizontally by approximately the same interval, 15 msec.

The results of these experiments demonstrate that during Wenckebach periodicity the function A′-H′ = f(H-A′) is not stable. Consequently, one cannot use a positive feedback mechanism that assumes that this function is stable in order to predict from the conduction time of one beat the conduction times of subsequent beats. We explored whether the function could be made more stable by including a second independent variable, such as the time from the blocked beat, the position of a beat within the cycle or the A-A′ interval. We were unable to find a function of two independent variables that was satisfactorily stable. Specifically, in four dogs the function A′-H′ = f(H-A′, A-A′) was studied when the A-A′ interval was held constant by plotting the A′-H′ versus H-A′ intervals for the beats after a test stimulus; in all four dogs the resulting curves were statistically distinct ($P < 0.01$). We conclude from these experiments that no positive feedback mechanism is operative during Wenckebach cycles that depends on a function describing the A′-H′ versus the H-A′ interval. It appears unlikely, also, that there is a feedback mechanism that depends on a function of two independent variables.

Studies in the isolated rat heart[27] showed that the effective refractory period after a beat occurred at a constant time interval after the ventricular depolarization of that beat and was independent of the previous history of the A-V conduction system. In Figure 6, the effective refractory period after various beats of the Wenckebach cycle does not occur at a constant H-A′ interval. It appears, therefore, that in the canine heart during Wenckebach cycles, one cannot adequately describe refractoriness as a function of the H-A′ interval alone.

Cumulative Effect

During 1:1 conduction when the frequency of atrial stimulation is abruptly changed to a new steady level, the A-H conduction time does not immediately jump to a new final value. Instead, a cumulative effect is seen; that is, a final value is approached through a series of intermediate steps. This effect has been seen in the canine and rabbit A-V nodes.[30,31] Heethaar et al.[32,33] described a similar phenomenon in the rat heart and found that one could describe the conduction time of the intermediate beats by means of an exponential equation.

During the Wenckebach phenomenon, the input frequency to the A-V node, the A-A′ interval, is constant and a cumulative effect could not occur on the basis of a change in input frequency. In a series of experiments, we studied whether one could find a cumulative effect after a blocked beat. Our reasoning was as follows: If, after a blocked beat, there was a slow increase in refractoriness of the A-V node during the subsequent series of beats, and if this increase in refractoriness were large enough to block another beat, then a self-sustaining cycle similar to a Wenckebach cycle would be established.

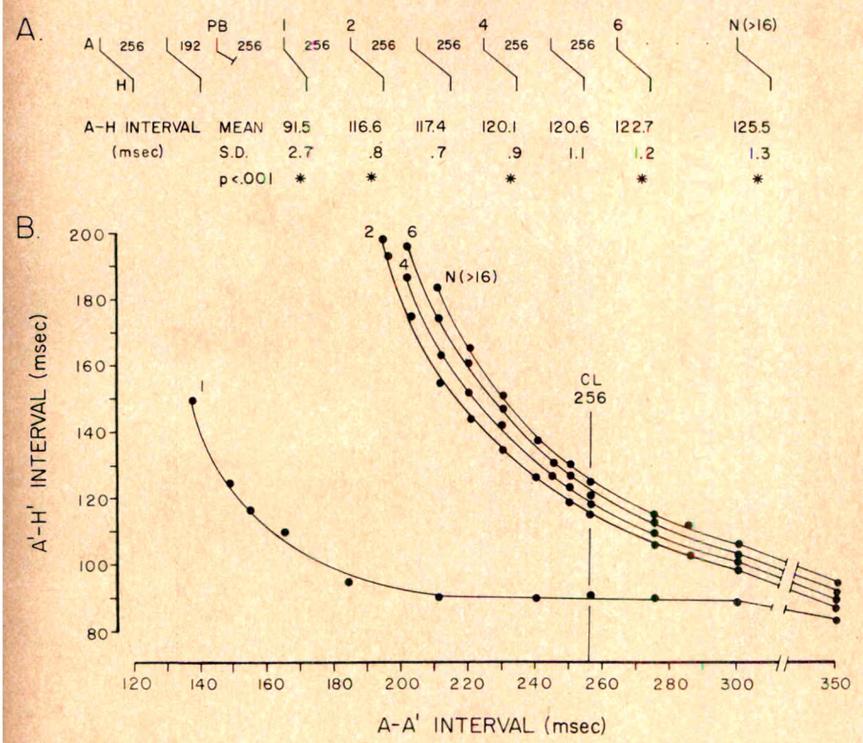

FIGURE 7. A, the pattern of stimulation used to study a cumulative effect during 1:1 conduction. At a basic cycle length of 256 msec a blocked premature beat (PB) was inserted at an A-A′ interval of 192 msec. Basic driving stimulation was immediately resumed. The A-H conduction times for the subsequent beats are listed. The nth beat (N) was more than 16 beats after the blocked premature beat. Each measurement represents the mean of 10 observations. p = probability; S.D. = standard deviation. **B,** refractory curves recorded when the test beat was inserted in various locations after the blocked premature beat. The conduction time for the test beat (A′-H′) is plotted against the test interval (A-A′). The basic cycle length (CL) is 256 msec Each point represents the mean of six observations.

We investigated this hypothesis in two series of experiments: First, during stressed 1:1 conduction, we explored whether one could find a cumulative effect on refractoriness and conduction time after a blocked beat. Second, we assayed the effect of a change in basic cycle length on the degree of cumulative effect to detect if, as the limit of 1:1 conduction is approached, the cumulative effect is large enough to spontaneously block another beat.

In the first set of experiments (*Fig. 7*) the heart was paced at a rate near the maximum rate permitting 1:1 conduction. No spontaneously blocked beats were observed during a 10 minute control period. Intermittently, after more than 16 basic driving beats, a premature beat was inserted at a time that was 10 to 20 msec less than the effective refractory period after the control beats. The premature beat was reliably blocked. Immediately after the premature beat, pacing resumed at the basic cycle length. Figure 7A diagrammatically represents the stimulation pattern in a typical experiment. The basic cycle length was 256 msec. The premature beat was inserted with a test interval of 192 msec. The conduction time for the nth or control beat, which occurred more than 16 cycles after the blocked premature beat, was determined. The conduction time for the first beat after the blocked premature beat did not immediately return to control; instead there was a gradual progressive increase in conduction times from the second beat (116.6 msec) to the nth beat (125.5 msec). Beats 3 to 6 after the premature beat had intermediate levels of conduction time. These results were significant (P <0.001). After a blocked premature beat during stressed 1:1 conduction there is a gradual progressive increase in conduction time.

We then explored whether the increase in conduction time was reflected in refractory curves (*Fig. 7B*). Refractory curves (A′-H′ versus A-A′ intervals) were drawn in a manner analogous to that in the Wenckebach studies. Figure 7B shows the refractory curves for beats 1, 2, 4 and 6 and for the nth beat from the same experiment as in Figure 7A. The conduction times observed during the control stimulation period are seen to be the results of the intersection of the basic cycle length with the refractory curves. It is also apparent that there is a progressive increase in refractoriness from the first to the nth beat as marked by an increase in A′-H′ conduction time for all the illustrated beats (P <0.005 for the A-A′ intervals 140 to 300 msec). The effective refractory period is shortest after the blocked beat and increases after the first beat to the nth beat (P <0.001). The largest increase in refractoriness occurs between the first and second beats; after the second beat there is a slow increase in refractoriness to the nth beat.

These experiments demonstrate that after a blocked premature beat the refractoriness of the A-V node shortens and does not immediately return to control value of refractoriness; instead there is a cumulative effect of a gradual increase in refractoriness lasting more than six beats. This experiment was performed in eight dogs with similar results. In seven of the eight dogs, the refractory curves for the second and nth beats were statistically distinct (P <0.01); in all eight dogs the refractory curves for the first beat were distinct from the second and nth beats (P <0.001). The refractory curves recorded in these experiments differed from those measured during the Wenckebach rhythm in two important aspects: First, the degree of increase of refractoriness from the second to the nth beat was less than that observed during Wenckebach periodicity. Second, although there was an increase in the duration of refractoriness from the first to the nth beat, it was not sufficient to cause the nth beat to block. The experiments were performed at 1:1 conduction and the nth beat continued to conduct; that is, the basic cycle length was longer than the effective refractory period after the n-1 beat (Fig. 7B). During Wenckebach phenomenon the effective refractory period after the last conducted beat exceeds the basic cycle length and the next beat is blocked.

A second set of experiments (*Fig. 8*) *was designed to explore the following two points:* (1) The effect of changes in

basic cycle length on the extent of the cumulative effect after a blocked beat, as marked by changes in the effective refractory periods for the subsequent beats. (2) The relation between the effective refractory period of the nth beat and the basic cycle length at different basic cycle lengths. These experiments were performed in a manner similar to those just described. The effective refractory periods were determined for the beats during Wenckebach cycles and for the series of beats after a blocked premature beat during stressed 1:1 conduction at different cycle lengths. The basic cycle lengths used were (1) the minimal basic cycle length that reliably produced 1:1 conduction, (2) a basic cycle length 15 msec longer, and (3) a basic cycle length that produced 4:3 Wenckebach periodicity. This experiment was performed in eight other dogs (Fig. 8). The mean results for testing only in the first, second and nth positions are shown diagramatically; the effective refractory periods for the intermediate beats had intermediate values.

During 1:1 conduction at the longer basic cycle length, 281.7 msec, the effective refractory period for the nth beat was a mean of 64.2 msec shorter than the basic cycle length (Fig. 8A). When the basic cycle length was shortened by 15.5 msec (Fig. 8B), the effective refractory period for the nth beat was found to be 33.8 msec shorter than the basic cycle length of 266.2 msec ($P < 0.001$). The effective refractory period for the nth beat rapidly approaches the basic cycle length because of both a decrease in basic cycle length and an increase in the effective refractory period; shortening the basic cycle length caused the effective refractory period for the nth beat to lengthen by 14.9 msec (217.5 to 232.4 msec). Because the nth beat occurs more than 16 beats after the blocked beat, the increase in refractoriness represents the effect of the change in basic cycle length on the general level of refractoriness of the A-V node.

When the basic cycle length was shortened further to 252.0 msec, reliable 4:3 Wenckebach periodicity ensued (Fig. 8C). Although there is no nth beat in a Wenckebach cycle, the effective refractory period after the last conducted beat of the cycle serves as an estimate of the minimal control level of refractoriness because refractoriness is increasing throughout the cycle. The effective refractory period after the third beat is 268.4 msec, longer than any effective refractory period recorded during 1:1 conduction, and represents a continuation of the rate-dependent increase in refractoriness. In the three experimental situations, as the basic cycle length decreases from 281.7 to 266.2 msec, then to 252.0 msec, the effective refractory period after the blocked beat lengthens (143.2 msec, 153.5 msec and 170.1 msec, respectively), as does the effective refractory period after the first beat (215.5 msec, 221.0 msec and 234.0 msec). The increase represents a general frequency-dependent change in refractoriness. A similar phenomenon was seen in Wenckebach cycles of various ratios discussed earlier (Fig. 4).

During the Wenckebach cycle, the basic cycle length is 16.4 msec less than the effective refractory period after the last conducted beat; consequently, the next beat, the fourth beat, is blocked. By design, the premature beat in the experiments during 1:1 conduction was inserted at a test interval that was less than the control effective refractory period by a similar degree (19 msec and 14 msec at cycle lengths of 281.7 and 266.2 msec, respectively). Hence the blocked premature beat during 1:1 conduction mimics closely the effects of the spontaneously blocked beat during the Wenckebach cycle.

The experiments at 1:1 conduction show that as the frequency of stimulation increases the cumulative effect also increases. At the longer basic cycle length, 281.7 msec, the cumulative effect was small. A change in the effective refractory period after the first beat to the effective refractory period after the nth beat was 2.0 msec (Fig. 8A). When the basic cycle length was shortened by 15.5 msec, the extent of the cumulative effect increased to 11.3 msec (Fig. 8B). An increase in the cumulative effect as the basic cycle length shortened was seen in all eight dogs ($P < 0.005$). When the basic cycle length was decreased further to 252.0 msec, producing 4:3 cycles, the difference between the effective refractory period after the first beat to that after the third beat was 34.4 msec. For each dog the difference was larger than the cumulative effects seen during 1:1 conduction ($P < 0.005$).

These experiments demonstrate that a cumulative effect is observable after a blocked premature beat during a stressed 1:1 conduction, that it increases as the frequency of stimulation increases and that a similar but larger phenomenon is observed during Wenckebach cycles. As the limit of 1:1 conduction is approached, it seems logical to extrapolate that the effective refractory period would at some time exceed the basic cycle length and a beat would spontaneously become blocked. The blocked beat would then establish a cumulative effect; that is, the refractoriness would immediately shorten and then return to its control level only after a series of conducted beats. If the basic cycle length were short enough, eventually the effective refractory period of the node would exceed the cycle length and another beat would become blocked. This sequence would establish a Wenckebach cycle.

The Wenckebach cycle appears to represent the interplay of three factors: (1) a rate-dependent increase in refractori-

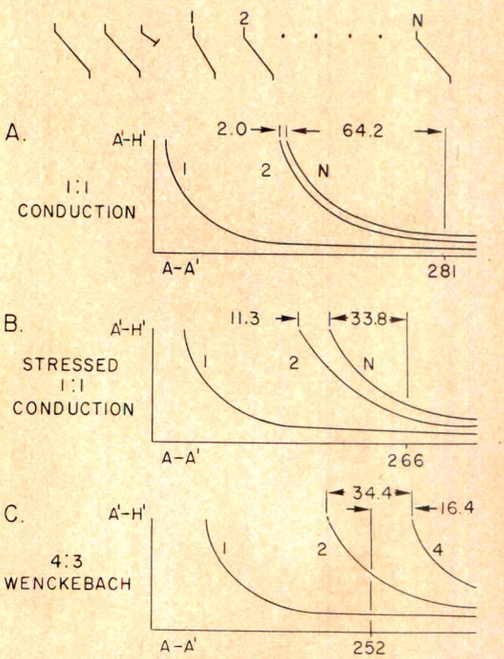

FIGURE 8. A and **B,** cumulative effect after a blocked premature beat as measured by a change in the effective refractory periods after the first and n-1 beats during testing at a basic cycle length of 281.7 msec **(A)** and 266.2 msec **(B).** The experimental protocol was similar to that depicted in Figure 7. The effective refractory period after the first beat is marked by the point on the curve for the second beat, which has the mimimal A-A′ test interval. The measurements in milliseconds represent the mean results of experiments in eight dogs. **C,** relation between the effective refractory periods after the first and third beats of a 4:3 Wenckebach cycle at a basic cycle length of 252.0 msec in the same eight dogs.

ness, (2) a shortening of refractoriness after a blocked beat, and (3) a cumulative effect after a blocked beat allowing a gradual increase in refractoriness. All three factors are seen during stressed 1:1 conduction. As the rate of stimulation increases during 1:1 conduction, both the control level of refractoriness and the cumulative effect increase in a manner that, if continued, would allow Wenckebach cycles to occur spontaneously. The effects of a blocked beat on subsequent refractoriness of the A-V node are essential to the mechanism of Wenckebach cycles.

Discussion

The refractory curves recorded during Wenckebach periodicity show that there is a progressive increase in refractoriness as the cycle proceeds and that during 4:3 Wenckebach cycles the A-V node repetitively advances through four distinct steps of increasing refractoriness. The blocked beat occurs because eventually a beat falls within the effective refractory period of the node. Refractory curves for all beats were smooth and without discontinuities, suggesting that dual pathways[34–36] through the A-V node were not involved in the production of Wenckebach cycles. The refractory curves had a continuously negative slope; therefore, any increase in refractoriness was qualitatively mirrored by an increase in conduction time.

Atypical Wenckebach Cycles

As classically defined,[16,17] typical Wenckebach cycles are marked by a progressive increase in A-V nodal conduction time, and the increment in conduction time continually decreases as the cycle proceeds. As a consequence of the progressive decrease in the increments in conduction time, the interval between ventricular depolarizations (R-R interval) decreases as the cycle advances.[17] Many observers[2,3,17,18] have noted that atypical Wenckebach cycles are frequently seen. This study offers several explanations for atypical cycles.

Small changes in the basic cycle length: The conduction times observed during Wenckebach cycles represent the intersection of the basic cycle length with the refractory curves. Small changes in the basic cycle length did not vary the refractory curves (Fig. 3) but had a large effect on the conduction time of the last conducted beat, the third beat, because the basic cycle length intersected the refractory curve for this beat at a steep portion of the curve. Consequently, small changes in the basic cycle length were magnified and caused much larger changes in the conduction time of the third beat. The most common feature of atypical Wenckebach cycles is that the conduction time of the last conducted beat is longer than expected.[2,17] The variability in conduction time of the last conducted beat reflects the fact that at the time of that beat the A-V node is very refractory and sensitive to the precise timing of the atrial input. Small, almost inapparent shifts in the basic cycle length can convert a typical cycle into an atypical one (Fig. 3).

Variable increase in refractoriness occurring during the Wenckebach cycle: This is a second reason for atypical cycles. Although conduction times of control Wenckebach cycles were typical in all dogs in our study, the increase in refractoriness as the cycle proceeded, as measured by the effective refractory periods, was frequently atypical. In 56 percent of the dogs (13 of 23) the effective refractory period did not increase with decreasing increments as the cycle advanced (Fig. 2). Moreover, the relation between the effective refractory period and conduction time is highly nonlinear, as can be seen by the shape of the refractory curves. The refractory curves, also, were not merely shifted rightward as the cycle proceeded, but changed shape; the curves for various beats were not superimposable. Because the observed conduction times in a Wenckebach cycle represent the intersection between the basic cycle length and the refractory curves, and because the refractory curves may vary in shape and position as the cycle proceeds, the increments of conduction time could also be highly variable. These studies demonstrate that a progressive decrease in the increments of conduction time is not at all a central feature of the Wenckebach arrhythmia. Because the increments of conduction time need not progressively decrease, the intervals between ventricular depolarizations need not also progressively decrease.

Fluctuations in the level of autonomic nervous system tone: This is another reason for the large incidence of atypical Wenckebach cycles. In our studies, the effects of the autonomic nervous system on the A-V node were minimized by interrupting the stellate ganglia and the vagi. Under these circumstances, it was found that the A-V node is quite precise. The mean standard deviation of the A-H conduction time for all dogs was 0.6 percent during 1:1 conduction. During Wenckebach cycles, the average standard deviation ranged from 0.7 percent for the first beat to 1.3 percent for the third beat. The precision of the denervated canine A-V node in our study exceeded the precision of commonly used electrophysiologic recording systems; speed variations of 15 percent have been reported for photographic paper recorders, for example.[37]

Changes in the tone of the autonomic nervous system can have marked effect on the sinus node rate and on the conduction time and refractoriness of the A-V node.[30,38] The effect of a change in autonomic tone on the Wenckebach rhythm could be complex and unpredictable for several reasons. First, altering the autonomic tone would produce changes in sinus rate and A-V nodal refractoriness that would produce opposing effects on Wenckebach cycles. An increase in vagal tone, for example, slows the sinus rate and thereby promotes Wenckebach cycles of longer conduction ratios, just as lengthening the basic cycle length does (Fig. 4). At the same time, a vagally induced increase in A-V nodal refractoriness would tend to produce Wenckebach cycles of a shorter conduction ratio because the refractory curves would shift rightward relative to the basic cycle length. The net effect of an increase in vagal tone would thereby be complex. Second, alterations in pulse pressure and cardiac output induced by the changing ventricular rate and the varying relation between atrial and ventricular depolarization during the Wenckebach cycle would alter autonomic tone.[39] Latency between the

change in autonomic tone and its effect on sinus rate or A-V nodal conduction time appears to be 200 to 450 msec.[28,40] As a consequence, the level of autonomic tone during a Wenckebach cycle could be continually varying in response to cardiac output changes induced by the cycle. Moreover, the autonomic nervous system receives inputs from diverse physiologic processes, such as respiration, which would independently influence the Wenckebach cycles.[39] Alteration in the tone of the autonomic nervous system is undoubtedly a frequent cause of atypical Wenckebach cycles.

Cumulative Effects in Wenckebach Cycles

A major purpose of our work was to document a cumulative effect after a blocked premature beat and to explore the relation between the cumulative effect and Wenckebach cycles. When the frequency of input stimulation to the A-V node is abruptly changed from one steady value to another, the conduction time and refractory period do not immediately follow the step in input frequency. Instead the conduction time and refractory periods for the beats after the frequency step show a gradual change to a new stable value. The change in conduction time and refractory period is usually the largest for the first beat after the step, and subsequent changes are smaller. This phenomenon, termed a cumulative or fatigue effect, has been observed in the conduction time and refractory period of the A-V node and in the refractory period of the atrium, His bundle and ventricular muscle.[31,32,41,42]

Cumulative effect after a blocked premature beat: Cumulative effects have usually been studied by changing the input frequency from one steady value to another. One purpose of our study was to document a cumulative effect after a brief transient perturbation, a blocked premature beat. A cumulative effect was seen for the effective refractory periods and conduction times of beats after a blocked premature beat during stressed 1:1 conduction (Fig. 8B). This effect was strongly dependent on frequency of stimulation and was apparent only during rapid rates of atrial stimulation. At slightly slower rates of stimulation, a cumulative effect was barely noticeable (Fig. 8A). Heethaar et al.[33] measured a similar cumulative effect after a blocked beat in the rat heart.

Cumulative effect on refractoriness: The cumulative effect observed after a blocked premature beat during stressed 1:1 conduction is intimately related to the production and maintenance of Wenckebach cycles. If the cumulative effect on refractoriness were large enough so that the A-V node would block another beat, then a self-sustaining cycle would be established. After a blocked beat, refractoriness shortens, and then only gradually increases because of a cumulative effect, allowing the beats after the blocked beat to conduct. Eventually refractoriness increases sufficiently to block another beat, which in turn establishes another cycle.

The logic of invoking a cumulative effect after a blocked beat in the production of Wenckebach cycles rests on the following observations: (1) Cumulative effects were seen at stressed 1:1 conduction that produced changes in the conduction time and refractoriness qualitatively similar to those observed during Wenckebach cycles. (2) Cumulative effects increased as the limit of 1:1 conduction was approached. (3) Because of a rate-dependent increase in the refractoriness of the A-V node, the effective refractory period rapidly converged on the basic cycle length as the limit of 1:1 conduction was approached. It seems logical to assume that with further shortening of the basic cycle length, the effective refractory period would exceed the basic cycle length, a beat would therefore block, and a cumulative effect would ensue, ending in another blocked beat.

The cumulative effect is most closely involved in the maintenance of Wenckebach cycles with conduction ratios greater than 2:1. If the cumulative effect were nonexistent, then the A-V node would not be able to sustain Wenckebach cycles with conduction ratios greater than 2:1. For example, if the A-V node had at all times a response to a blocked beat similar to that demonstrated in Fig. 8A, i.e., little or no further increase in refractoriness after the first conducted beat following the blocked beat, then the A-V node would be able to sustain only 2:1 cycles. After the first beat of the cycle, the node would immediately return to its control level of refractoriness, which would have to be in excess of the basic cycle length if beats were to block spontaneously. Hence, every other beat would block, and only 2:1 cycles could be maintained. The refractory curves in this situation would be expected to be similar to the 2:1 cycles recorded in Figure 4.

Electrophysiologic Mechanisms

Although the electrophysiology of the A-V node is not fully understood, two mechanisms are likely to be important in the production of a cumulative effect: (1) the effect of electrotonic interactions on the refractoriness of the cells of the A-V node, and (2) intrinsic, frequency-dependent changes in the duration of refractoriness of A-V nodal cells.

Electrotonic interactions and refractoriness of A-V nodal cells: The A-V node functions as a syncytium with electric interconnections between cells that allow them to pass current from one to another, thereby interacting with each other.[4,43,44] These interactions, termed electrotonic interactions, allow a cell that depolarizes, for example, to supply depolarizing current to neighboring cells, thereby depolarizing them to a variable degree. If the neighboring cells do not fully depolarize, they in turn will supply repolarizing current back to the original cell, thereby tending to repolarize it. Electrotonic interactions are thought to be responsible for shortening the action potential duration of cells at the edge of an arrested wave front of depolarization and prolonging the action potential duration of cells at the edge of a slowly conducting wave front of depolarization.[43]

Mendez and Moe[43] demonstrated that there is a correlation between action potential duration and the duration of refractoriness. After an abbreviated action potential, arising from a blocked beat, the duration of

refractoriness is shorter than after a normally conducted beat with a longer action potential duration. Conversely, there is a longer duration of refractoriness when the action potential duration is prolonged by slow conduction.

A cumulative effect could be explained in terms of electrotonic interactions and action potential duration in the following manner[8]: The blocked beat enters the A-V node and blocks at a variable distance within the node. The action potential duration of the cells that conducted the beat is shortened because of electrotonic interactions. The refractoriness of the node therefore is relatively less than normal because the action potential duration of the cells that conducted the beat is shortened and because the more distal portions of the A-V node are not fully depolarized. Consequently, the first beat after the blocked beat conducts in the node reasonably rapidly. The action potential duration of the first beat is longer than that after the blocked beat because there are no electrotonic interactions tending to shorten it. Because the action potential duration is longer, the second beat finds the cells of the A-V node more refractory. Therefore the second beat conducts even more slowly, and the action potential duration of the second beat is even longer. Consequently, the third and successive beats find the A-V node even more refractory. Because cells conducting slowly have a longer action potential duration as a results of electrotonic interactions and because action potential duration influences the duration of refractoriness, successive beats would conduct progressively more slowly and would, in turn, promote progressively more refractoriness. Depending on the degree to which action potential duration and the duration of refractoriness interact, the A-V node would either become sufficiently refractory to block another beat, as in Wenckebach cycles, or stabilized to a final value of increased refractoriness, as in the cumulative effect seen after a blocked beat during 1:1 conduction. In support of the theory of electrotonic interactions, microelectrode studies of cells during Wenckebach conduction[4,5,7] have shown shortening of action potential duration for the blocked beat and then a progressive increase in action potential duration for the subsequent beats.

Intrinsic, frequency-dependent changes in duration of refractoriness of A-V nodal cells: A second explanation for the cumulative effect may lie in the delayed recovery of electrical excitability of A-V nodal cells. With direct intracell stimulation of A-V nodal cells, Meredith et al.[31] found that the recovery of excitability lags behind full electrical repolarization by as much as several hundred milliseconds. A lag in recovery is not seen in other cardiac cells under normal circumstances, and these data provide one line of evidence that the physicochemical basis for the action potential in the A-V nodal cells differs from that in other cardiac cells and may involve a slow channel calcium-dependent mechanism.[45,46]

As the frequency of stimulation increases, the lag in recovery of electrical excitability prolongs and the threshold for electrical excitability increases.[31] The time courses for the increase in the delay of recovery of electrical excitability and for the increase in diastolic threshold after a frequency step or after a blocked premature beat are unknown. By analogy to the increased conduction time and the increased effective refractory period of the A-V node with increasing frequency of stimulation, one might conclude that the lag in recovery and the diastolic threshold of individual cells may show cumulative effects. In other words, cells distal to a blocked beat may decrease their delay in recovery of excitability and diastolic threshold, and with subsequent beats only gradually increase these variables. Hence, the cumulative effect after a blocked beat for the conduction time and the effective refractory period of the entire A-V node may mimic and be due to changes in excitability occurring at the cell level.

Positive Feedback

The mechanisms discussed so far involve the concept of positive feedback, that is, a means by which a change in a given function (the slowing of conduction) engenders a process (increased refractoriness) that in turn causes a further change in the same direction of the original function (further slowing of conduction). The concept of positive feedback has been extensively applied to Wenckebach cycles by Levy et al.[11,12] One could consider the cumulative effect for the conduction time and effective refractory period after a blocked beat to be a manifestation of a self-limited form of positive feedback.

In our studies, the conduction time through the A-V node, the A-H interval, could not be expressed in terms of a positive feedback process with the diastolic interval, the H-A′ interval, as the sole independent variable. The function $A'\text{-}H' = f(H\text{-}A')$ was not stable throughout the Wenckebach cycles, and consequently one could not use it to predict subsequent conduction times. This finding does not invalidate the concept of positive feedback; rather it indicates that it should not be applied literally. There appear to be multiple determinants of conduction time through the A-V node, and this is not surprising in view of the complexity of A-V nodal conduction involving many elements that may combine in a highly nonlinear fashion: the complex geometry,[37] inhomogeneous conduction pathways,[6,7] summation,[5,44] the variable length of conduction pathways,[7,25] a poorly defined physicochemical basis for electrical activity within the cells,[45,46] electrotonic influences on repolarization and delayed recovery of excitability,[8,31,43] and so on.

Reentry During Wenckebach Cycles

In these studies we found no evidence for overt or concealed reentry during anterograde Wenckebach cycles. Unambiguous evidence for concealed and manifest reentry has been documented during retrograde Wenckebach cycles in the canine heart, and during anterograde and retrograde cycles in the rabbit and in the human A-V node.[6,9,10,18,19] It has been suggested by Damato and co-workers[9,10] that concealed reentry occurs continuously throughout Wenckebach cycles; they

interpreted notches seen on the action potential of A-V nodal cells during Wenckebach cycles as evidence of reentry. However, others[4,7,19,24,43] have thought that notches during the action potential of A-V nodal cells were due to electrotonic influences during slow conduction.

It appears most likely that Wenckebach cycles and reentry are associated conditions, not necessarily causally related. The critical prerequisites for reentry appear to be (1) multiple pathways through the A-V node, (2) at least one pathway must be sufficiently refractory so that an impulse blocks in that pathway and reenters it at a later time in the opposite direction.[9,10,34,48,49] As the A-V node becomes increasingly refractory during a Wenckebach cycle, these conditions could be met and reentry could occur. The reentrant beat could then terminate the Wenckebach cycle by collision with the next impulse. However, the underlying mechanism for the reentrant beat is the increasing refractoriness as the Wenckebach cycles proceed; the reentrant beat is the effect and not the cause.

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Myocardial Hemorrhage After Coronary Reperfusion in Pigs

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The effects of 1 hour of occlusion of the left anterior descending coronary artery and subsequent reperfusion were studied for 3 hours in anesthetized closed chest pigs using an intracoronary balloon occluding technique. In 12 pigs subjected to reperfusion, S-T segment elevation decreased to control levels within 30 minutes and was significantly less than in 10 control pigs without reperfusion ($P < 0.05$). R wave amplitude was unaffected by the reperfusion. The more rapid fall of S-T segments in the reperfused group was accompanied by major hemorrhage in all reperfused hearts; hemorrhage occurred in only one control heart. The extent of hemorrhage was quantified and was significantly greater in the reperfused than in the control group ($P < 0.01$). Hemorrhage after reperfusion was unaffected by mannitol-induced increase in serum osmolality but was greatly decreased by limitation of the occlusion period to 15 minutes. Myocardial wall motion was quantified angiographically. Shortening fraction of the area of the left ventricle most severely affected by occlusion decreased to similar levels in both groups. After reperfusion it remained similar in both groups at three hours. Adjacent left ventricular areas were likewise unaffected by reperfusion.

This study thus documents the occurrence of postreperfusion myocardial hemorrhage in an animal with a coronary circulation similar to man's. Hemorrhage is directly related to the duration of occlusion but appears to be unaffected by mannitol given before reperfusion. Caution is advised both during bypass surgery, in which occlusion and reperfusion occur, and in efforts to restore coronary blood flow during acute myocardial infarction.

Coronary bypass surgery performed during acute myocardial infarction is a logical therapeutic maneuver undertaken to salvage ischemic myocardium and preserve myocardial function. Reports of bypass surgery in patients with acute infarction or ischemia have shown that the procedure is technically feasible and can be undertaken at an acceptable operative risk.[1–6] Despite the expected difficulty in defining an adequate control group for these observations, clinical improvement,[1–6] reversal of electrocardiographic evidence of ischemia[2] and serial improvement of segmental dysfunction[6] in those patients surviving surgery have suggested an improvement in ischemic myocardium. However, a recent report[7] of hemorrhagic necrosis in the myocardium served by patent bypass grafts indicates that the results of reperfusion during the course of myocardial infarction in man are not fully known.

Experimental studies in animals, performed to define the conditions under which potential benefits can be realized, have had widely divergent results. Segmental wall motion has been shown to be improved[6,8,9] or worsened[10–13] and infarct size decreased[8,14–17] or increased.[18] Intramyocardial hemorrhage, sometimes of massive proportions, has been reported and has been correlated with the duration of the preceding cor-

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onary occlusion.[10,15,17,18] Although such hemorrhage has been thought to be related to direct disruption of vascular integrity,[19] Diaz et al.[20] reported a greatly reduced incidence of postreperfusion hemorrhage in the anesthetized or propranolol-treated dog, suggesting that reduced sympathetic tone under these circumstances may be responsible for this observation.

The applicability of experimental studies to man may be directly dependent on the animal model used. Our study of the effects of coronary reperfusion on intramyocardial hemorrhage, segmental wall motion and the precordial electrocardiographic map was therefore carried out in the pig, which has a heart similar to man's.[21–24]

Methods

Thirty-eight farm-bred pigs were anesthetized with chlorolose, 60 mg/kg body weight, and sodium pentobarbital, 35 mg/kg intravenously and placed supine. A precordial electrocardiographic map of 18 electrodes was recorded as previously described.[25] Three leads from the map were recorded simultaneously at double standard (1.0 mv = 20 mm) and at a paper speed of 25 mm/sec on an eight channel recording system. S-T segment elevation was measured 0.1 second beyond the beginning of the QRS complex; mean S-T elevation and mean R wave amplitude were calculated.

Femoral arterial pressure was monitored with a Statham P23Db pressure transducer. A no. 7F Eppendorf catheter, introduced through the other femoral artery, was passed retrograde into the left ventricle. Cardiac output determination was carried out using either the thermodilution technique with a thermistor catheter in the pulmonary artery or the indocyanine green technique with dye injection into the pulmonary artery and femoral arterial sampling. Arterial blood gases were monitored to assess the adequacy of ventilation; animals were rejected for study if the initial arterial partial pressure of oxygen (PO_2) was less than 80 mm Hg; if evidence of hypoxia developed during the study, supplemental oxygen was given to maintain PO_2 between 80 and 100 mm Hg.

Left ventriculograms were recorded in a 30° right anterior oblique projection. Fifteen to 20 cc of sodium and meglumine diatrizoates (Hypaque-M 75 percent®, Winthrop Laboratories) was power-injected over 2 seconds while 35 mm cine film was exposed at 60 frames/sec using a 6 inch image intensification system.

Occlusion technique: Details of the technique for coronary occlusion have previously been described.[25] In brief, a no. 8F thin-walled catheter was guided fluoroscopically into the left anterior descending coronary artery and 1 cc of sodium and meglumine diatrizoates was injected to permit visualization of its length and course. A no. 3F embolectomy catheter (Edwards Laboratories) was passed through the larger catheter into the left anterior descending coronary artery and the outer catheter was then withdrawn into the aorta. The tip of the catheter was positioned in a similar location in all animals: two thirds of the distance between the origin of the left anterior descending coronary artery and the inferior border of the heart. This position was always beyond the largest septal perforating vessel.

Protocol: Animals were randomly assigned to the reperfusion group (no. = 12) or to the nonreperfused control group (no. = 10). Control measurements were made of the precordial map, arterial blood gases, cardiac output, heart rate and arterial blood pressure. A left ventriculogram was next performed, completing the control condition. Hemodynamic and blood gas measurements were repeated at 60, 90, 120 and 180 minutes. Ventriculography was repeated at 60, 90 and 180 minutes. S-T segments were measured at 5, 10, 15, 30, 45 and 60 minutes, similarly during the second hour, and at 150 and 180 minutes. Precordial R wave amplitude was measured in the control period and at 60, 75 and 180 minutes.

Reperfusion was carried out in the reperfusion group immediately after the 60 minute measurements by abruptly deflating the coronary occlusion balloon and withdrawing the catheter into the aorta.

Pathologic analysis: The left ventricle was sectioned into seven slices by cuts placed perpendicular to an imaginary line extending between the left ventricular apex and aortic valve. Each slice was divided into five portions (septum and anterior and posterior right and left ventricles); the free ventricular portions were further divided into epicardial and endocardial portions and the septum into right and left ventricular portions. Each of these portions was examined for hemorrhage and scored as follows: 1 point for scattered involvement of less than 25 percent, 2 points for continuous involvement of less than 25 percent, 3 points for scattered involvement constituting 25 to 50 percent of the portion, 4 points for continuous involvement of 25 to 50 percent, and 5 points for continuous involvement of more than 50 percent. The score for each animal was obtained by summing all points.

Ventriculographic analysis: Left ventricular wall motion was analyzed by comparing the end-systolic and end-diastolic ventricular outlines during contrast opacification of the chamber. Analysis was carried out in a manner that corrected for rotation of the ventricle as follows: (1) A longitudinal reference line was drawn on the end-diastolic frame from the ventricular apex to the junction of the aortic and mitral valves. This junction is fibrous, noncontractile and easily identifiable, and it therefore served as a reliable reference point. (2) A similar reference line was drawn on the end-systolic frame. (3) Each longitudinal axis was divided into four equal segments by three hemiaxes drawn perpendicular to it; these hemiaxes were extended to the outline of the opacified ventricular chamber as previously drawn, thereby dividing the chamber into eight sectors.

The change in planimetered sector area was used to describe wall motion. Shortening fraction (SF) (percent) for each segment was calculated according to the formula:

$$SF = (A_{ed} - A_{es})/A_{ed} \times 100$$

where A_{ed} = end-diastolic sector area and A_{es} = end-systolic sector area.

This report describes the changes occurring in three sectors of each ventriculogram: the sector showing major depression secondary to the coronary occlusion and those two sectors adjacent to the major sector. The former was defined as that sector showing the most marked depression of the S-T segment at 1 hour when compared with the preocclusion state. The adjacent sectors were located, one superior to and one inferior to the major sector. If the latter was at the apex, the two adjacent sectors were located above and lateral to it.

Early release group: Seven animals underwent a similar coronary occlusion with reperfusion at 15 minutes. These animals were observed over the next 2 hours. They were then killed and their hearts studied pathologically to determine the effect of this brief occlusion on the incidence and extent of myocardial hemorrhage.

Mannitol group: Mannitol (62.5 g) was given to nine additional animals to examine its effect on the incidence or extent of myocardial hemorrhage. It was administered by constant infusion 30 to 45 minutes after occlusion, resulting in a significant rise of serum osmolarity, 30 ± 9 (standard error of

TABLE I

Hemodynamics Before and After Coronary Occlusion in Pigs With Reperfusion or No Treatment (Control) 60 Minutes After Occlusion (mean ± standard error of the mean)

	no.	Control	Minutes After Occlusion 60	90	120	180
Heart rate (beats/min)						
Control	10	160 ± 14	194 ± 13	187 ± 10	174 ± 8	190 ± 15
Reperfusion	12	150 ± 5	156 ± 9*	155 ± 6*	165 ± 7	171 ± 6
Mean arterial blood pressure (mm Hg)						
Control	10	139 ± 4	144 ± 6	140 ± 6	140 ± 3	114 ± 6†
Reperfusion	12	141 ± 6	153 ± 6	153 ± 5	142 ± 3†	137 ± 5†*
Cardiac output (liters/min)						
Control	10	4.2 ± 0.6	3.4 ± 0.3	3.5 ± 0.4	3.4 ± 0.4	3.4 ± 0.3
Reperfusion	12	3.7 ± 0.4	3.1 ± 0.3	2.9 ± 0.3	3.2 ± 0.4	3.7 ± 0.5

* $P < 0.05$ (between control and reperfusion groups).
† $P < 0.05$ (between value at 60 and those at 90,120 and 180 minutes within each group).

the mean) mOsm from baseline ($P < 0.05$). Reperfusion was then carried out at 1 hour and continued for a 2 hour period as in the control and reperfusion groups.

Statistical analysis: Data were analyzed using Student's *t* test for group data and for paired data where changes in each animal were examined. $P < 0.05$ was considered the lower level of significance.

Results

Hemodynamics (Table I): Heart rate was similar for both the control and reperfusion groups before occlusion. After occlusion, heart rate increased in the control group, resulting in a significant difference from values in the reperfusion group at 60 and 90 minutes after occlusion. Heart rates of both groups were similar for the remainder of the study, remaining slightly higher in the control group. Arterial pressure was similar in both groups except at 180 minutes, when mean arterial pressure was lower in the control group, thus coinciding with a tendency toward a higher heart rate in this group. Cardiac output was similar in both groups during the control period and remained so throughout the study. These measurements were examined within each group to detect serial changes occurring after 60 minutes. Comparison of the values at 90, 120 and 180 minutes with that at 60 minutes showed no changes in heart rate or cardiac output. There was a significant decrease in arterial pressure in both groups terminally.

Prevalence of hemorrhage (Fig. 1): Scores indicative of the severity and extent of hemorrhage ranged from 0 (no hemorrhage) to 72 for all 22 animals in the study. Of the 10 control animals, 6 were without hemorrhage, and only 1 had hemorrhage of major proportions (score 41); one had a small area of confluent septal hemorrhage and one a few spotty areas of septal hemorrhage. In the latter two hearts, the hemorrhage was confined to only one section. One heart in the control group was not available for examination. The mean score for the control group was 4 ± 4 (mean ± standard error of the mean). In contrast, 10 hearts from the 12 animals subjected to reperfusion alone were available for examination, and all showed extensive hemorrhage in the septal and anterior left ventricular walls, with occasional extensions seen into the posterior left ventricle and anterior right ventricle. Scores ranged from 9 to 72, with a mean of 25 ± 6. There was a highly significant difference between the scores of the reperfusion and control groups ($P < 0.01$).

Reperfusion in the nine animals with increased osmolarity due to prior mannitol infusion did not result in a lesser incidence of hemorrhage than in the animals

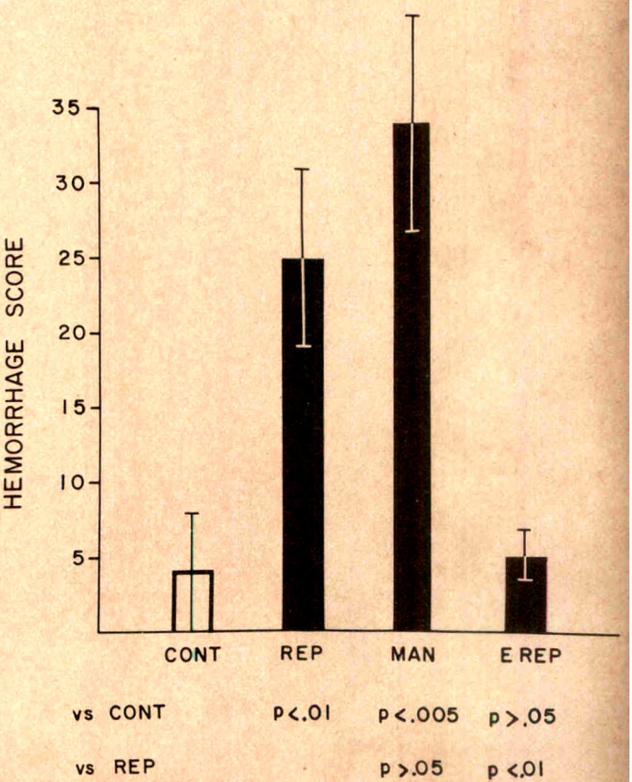

FIGURE 1. Hemorrhage score for control (CONT), reperfusion (REP), and mannitol (MAN) groups as well as for the group with early reperfusion (E REP). Statistical comparisons made with control (vs CONT) and with reperfusion (vs REP) groups are indicated below the bars. See text for the details of score calculation.

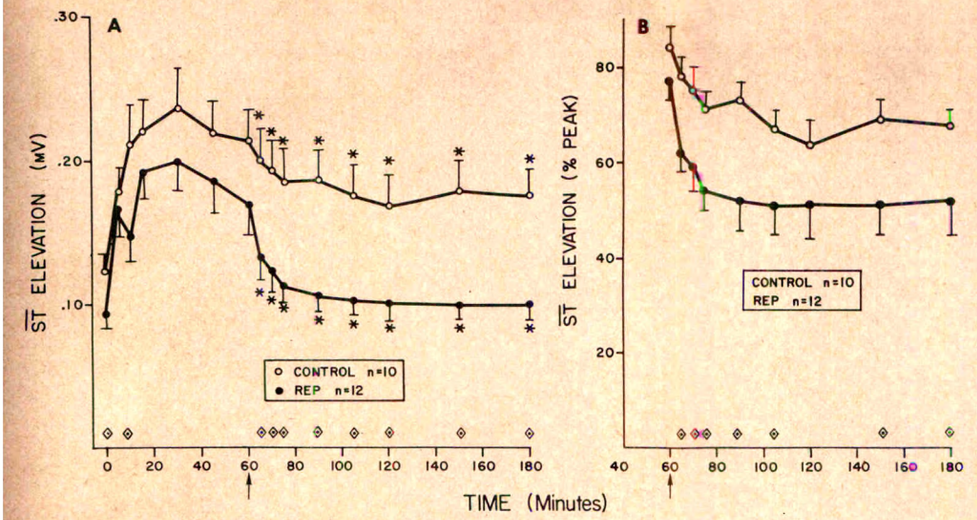

FIGURE 2. Mean S-T segment elevation (ST) ± standard error of the mean in the control and reperfusion (REP) groups. Values are in millivolts (mV) for the entire study **(A),** and in percent of peak S-T elevation for the period 60 to 180 minutes **(B).** Release of coronary occlusion at 60 minutes in the reperfusion group is indicated by the **vertical arrow.** In **A,** significant change from the 60 minute value ($P < 0.05$) within each group is indicated by an **asterisk** (*); significant difference between the two groups is indicated by a **diamond** (◊). In **B,** statistical analysis is carried out only between the two groups.

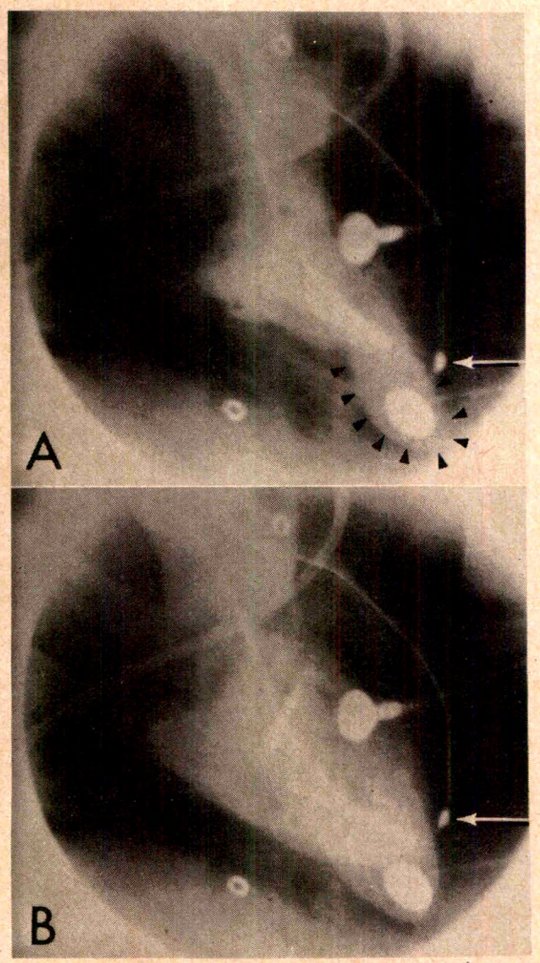

FIGURE 3. End-systolic **(A)** and end-diastolic **(B)** frames from the ventriculogram of one animal 60 minutes after occlusion, immediately preceding reperfusion. The **black arrows** identify an apical akinetic area that developed after the occlusion. Note the balloon occluder and catheter, opacified by contents of mercury **(white arrow).**

in the reperfusion alone; all eight hearts available for examination had extensive areas of hemorrhage with scores ranging from 8 to 59 with a mean 34 ± 7 ($P > 0.05$ mannitol versus reperfusion groups).

In the early reperfusion group (seven animals), four showed no hemorrhage and three small amounts of hemorrhage, with scores of 17, 9 and 6, respectively. The mean score of 5 ± 2 was significantly different from that of the reperfusion group ($P < 0.01$) and similar to that of the control group ($P > 0.05$).

Precordial mapping (Fig. 2, Table II): S-T segment changes were characterized by a rapid elevation from control level after occlusion, reaching a peak 30 minutes after occlusion. During the second and third hours, both groups demonstrated significant ($P < 0.001$) but unequal rates of decline from the 1 hour value. In the reperfusion group, mean S-T elevation returned to the preocclusion level within 30 minutes after reperfusion ($P > 0.05$); in the control group it continued elevated for the duration of the study and remained significantly above the level in the reperfusion group.

These differences can be further analyzed by consideration of mean S-T elevation as a percent of peak S-T elevation thereby discounting the small differences in peak values (Fig. 2B). After reperfusion, the mean S-T elevation of the reperfusion group decreased 16 percent from the peak level within 5 minutes and 24 percent from the peak level within 15 minutes. Although similar to values in the control group just before reperfusion, the mean S-T elevation as a percent of peak elevation remained significantly less than values in the control group except for one measurement made after reperfusion.

R wave amplitude (Table II) was similar in both the control and reperfusion groups during the control period and decreased significantly in both groups after occlusion. It remained depressed for the remainder of the study and was statistically similar in both groups.

TABLE II

R Wave Amplitude (mv) (mean ± standard error of the mean)

Period	Control Group	P*	Reperfusion Group	P*	P†
Control	0.71 ± 0.22	. . .	0.65 ± 0.16	. . .	>0.05
Postocclusion					
60 minutes	0.39 ± 0.14	<0.03	0.45 ± 0.13	<0.003	>0.05
75 minutes	0.34 ± 0.21	<0.02	0.34 ± 0.10	<0.01	>0.05
180 minutes	0.26 ± 0.13	<0.01	0.30 ± 0.09	<0.05	>0.05

* Versus control period.
† Control versus reperfusion group. *P* = probability.

Left ventricular wall motion: An end-systolic and end-diastolic frame from the left ventriculogram of one animal is shown in Figure 3. Taken at 60 minutes, immediately before reperfusion, it shows an akinetic apex with good motion of the adjacent areas.

Group analysis of wall motion (Fig. 4) showed that the most depressed segment in each group was similarly depressed at 60 minutes (before reperfusion), with a shortening fraction of 5 ± 6 percent for the control and 11 ± 6 percent for the reperfusion group ($P > 0.05$). When compared at 90 minutes, shortening fraction was significantly lower in the control than reperfusion group (−4 ± 7 percent versus 15 ± 5 percent, $P < 0.025$), in part related to worsening of the control group wall motion. At 180 minutes both groups were once again comparable (9 ± 8 percent versus 11 ± 6 percent, $P > 0.05$). There were no significant changes *within* either group when shortening fraction at 60 minutes was compared with measurements at 90 or 180 minutes ($P > 0.05$).

In the adjacent sectors, there existed no differences between the control and reperfusion groups at any time during the study (Fig. 5). There were no changes *within* either group when shortening fraction at 60 minutes was compared with measurements at 90 or 180 minutes.

Discussion

Previous experimental observations: The occurrence of postreperfusion myocardial hemorrhage in the setting of experimental acute myocardial infarction is well known. Bresnahan et al.[18] found that 7 of 16 dogs undergoing reperfusion 5 hours after infarction demonstrated extension of their infarct after reperfusion; this extension was associated with myocardial hemorrhage in all 7 animals. Lang et al.,[10] studying closed chest dogs undergoing reperfusion after 3 hours of occlusion, found intramyocardial vascular congestion and hemorrhage in all of six animals with pathologic evidence of myocardial infarction. Mathur et al.[15] noted hemorrhagic infarction in "most of the reperfused groups" although infarct size was reduced when reperfusion was carried out at 2 rather than at 5 hours. Similar results have been reported in rats undergoing reperfusion at 6 hours rather than at 1 hour.[17] However,

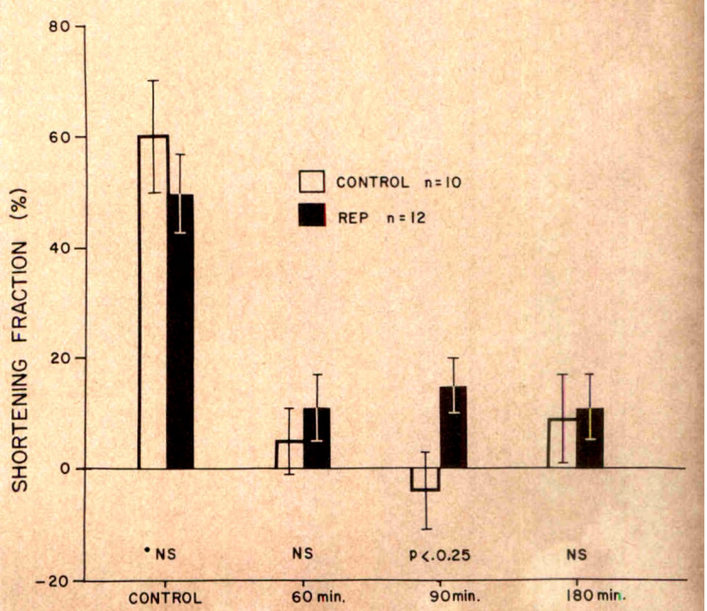

FIGURE 4. Shortening fraction of the most depressed left ventricular segment (mean ± standard error of the mean). Significance of changes between control and reperfusion (REP) groups is indicated below each bar. Comparison of the 90 and 180 minute values with the 60 minute value within each group showed no significant differences ($P > 0.05$). NS = not significant; p = probability.

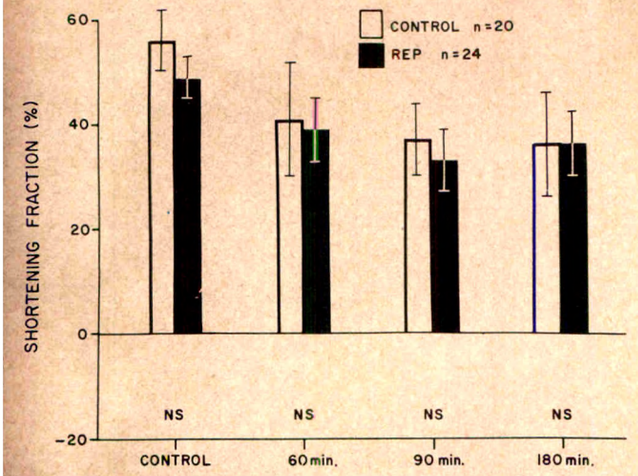

FIGURE 5. Shortening fraction of the adjacent ventricular segments (mean ± standard error of the mean). Significance between the control and reperfusion (REP) groups is indicated below each bar group. Comparison of the 90 and 180 minute values with the 60 minute value within each group showed no significant difference ($P > 0.05$).

others have failed to comment upon the presence of hemorrhage after reperfusion.[8,9,14,16] In fact, Maroko and co-workers[8] reported that the hearts of dogs reperfused after 3 hours of occlusion demonstrate preservation of structural integrity histologically and reduction of infarct size at 24 hours as well as marked reduction in the necrotic area 7 days after reperfusion.[16] This lack of agreement among investigators concerning postreperfusion hemorrhage may be related to differences in species of animals used or to differences in experimental design; it suggests that the effects of reperfusion on myocardial hemorrhage are far from understood.

Intramyocardial hemorrhage after reperfusion in the pig: In this study of reperfusion we used the pig as the experimental model because its heart is similar to man's in weight, coronary circulation and collateralization.[21–23] The pig also shows less interanimal variation in coronary anatomy and distribution than the dog[24] and predictably has a myocardial infarction after coronary occlusion. Closed chest conditions were used to avoid alteration of cardiac function associated with open chest preparations. Myocardial reperfusion in the pig 1 hour after occlusion of the distal third of the left anterior descending coronary artery consistently resulted in massive intramyocardial hemorrhage. This was in contrast to little or no hemorrhage found in the control group animals. The hemorrhagic phenomenon appeared to be time-dependent because it did not occur to a significant degree in seven animals undergoing reperfusion after only 15 minutes of coronary occlusion. The absence of hemorrhage in the latter group also indicates that the hemorrhage was not a consequence of the occlusion technique itself. It therefore appears that in the pig the critical period with respect to intramyocardial hemorrhage lies between occlusion times of 15 and 60 minutes.

Mechanisms of intramyocardial hemorrhage: The mechanism for such hemorrhage may relate to disruption of capillary integrity during myocardial ischemia[19] followed by leakage of red cells during the reflow period. Diaz et al.[20] reported an association between autonomic tone and postreperfusion myocardial hemorrhage. They found extensive hemorrhage in 15 of 17 dogs undergoing reperfusion in the awake state but in only 3 of 16 anesthetized dogs undergoing reperfusion. Decreased autonomic tone due to general anesthesia was postulated as the basis for the decreased incidence of hemorrhage because a similar reduction of hemorrhage was also seen in conscious dogs pretreated with propranolol before reperfusion. In contrast, we found that general anesthesia offered no protection against postreperfusion hemorrhage. Moreover, a recent report, has suggested that these findings may be applicable to human beings undergoing coronary bypass surgery during other than acute conditions. Bulkley et al.[7] studying the hearts of patients who died within 30 days of coronary bypass surgery described necrosis, primarily of the hemorrhagic contraction band type, in the majority of myocardial areas subserved by patent bypass grafts. However, hemorrhage was infrequent in those areas subserved by an occluded graft. Thus the transient ischemia that occurs during surgery may predispose to myocardial hemorrhage in the same manner as during reperfusion after an acute occlusion.

Effect of mannitol: No reduction in hemorrhage occurred when mannitol was given before reperfusion despite reports that this agent reduces myocardial cell swelling and coronary vascular resistance due to myocardial ischemia[26] and increases collateral blood flow into ischemic myocardium.[27–29] Our observations are consistent with the lack of improvement of mitochondrial function after reperfusion in mannitol-treated pigs.[30] It further suggests that mannitol is less effective in increasing collateral flow before reperfusion in the pig than in the dog, possibly because of near complete ischemia in the porcine infarct area restricting the access of therapeutic agents to the reperfused zone.[31]

Effect of reperfusion on hemodynamics: In general, hemodynamics were not affected by the reperfusion process. Heart rate in the control group was unaccountably higher than in the reperfusion group despite the similarity in the animals and in the experimental procedure during the first hour of the study and the randomization of animals into the two study groups. This difference in heart rate is compatible with a smaller area of ischemia in the reperfusion group, which also tended to have less S-T elevation during the first hour than the control group. Nevertheless, such differences are probably slight because the degree of wall motion abnormality at 60 minutes was comparable in both groups.

Effect of reperfusion on ventricular wall motion examined angiographically: We observed no improvement in function of either the most depressed left ventricular segment or adjacent segments during re-

perfusion. Some investigators have agreed and others disagreed with this finding. Maroko et al.[8] found reversal of paradoxical ventricular motion 1 hour after reperfusion in the dog, whereas Banka et al.,[10] using a similar protocol, observed marked deterioration in left ventricular wall motion at this time. In the very acute infarct-reperfusion setting, Smith et al.,[13] using ultrasonic myocardial sensors, found immediate recovery of function in the dog after reperfusion followed by rapid deterioration of wall motion. In a more prolonged study of dogs, Theroux et al.[32,33] found initial deterioration (at 2 hours) of wall motion but at 3 weeks noted greater recovery of function in animals undergoing reperfusion. Similarly, McNamara et al.,[9] using a ventriculographic technique, found improvement in left ventricular wall motion in seven of nine monkeys 7 days after reperfusion; however, a nonreperfused control group of three monkeys also showed improved wall motion at 1 week.

Recovery of function has been linked to the duration of coronary occlusion preceding the reperfusion. Hendricks et al.,[12] using a brief 5 minute occlusion, found continued depression of wall motion 3 hours after reperfusion, whereas recovery was delayed more than 6 hours after reperfusion if coronary occlusion was increased to 15 minutes in duration. In canine myocardial pedicle grafts recovery of function did not occur if coronary occlusion was extended beyond 30 minutes.[34] Recovery of ventricular wall motion after reperfusion in dogs failed to occur after occlusion times of more than 45 minutes when studied using Walton-Brodie strain gauge measurements[10] or after 2 hours using a ventriculographic analysis of wall motion.[6] Although investigators disagree on the wall motion abnormality after reperfusion, most conclude that failure of improvement or actual deterioration of wall motion occurs acutely and is directly related to the duration of the preceding occlusion. There appears to be some evidence for long-term improvement of left ventricular function if one considers those animals that survive beyond the acute period.[9,16,33]

Precordial electrocardiographic mapping: The failure of wall motion to improve in our study is in marked contrast to the significant reduction in S-T segment elevation after reperfusion. Similar observations regarding S-T segment changes in open chest dogs,[8] rats[17] and primates[14] have previously been used as indirect evidence of reduction of infarct size. However, R wave voltage, previously noted to correlate well with the degree of histologic necrosis,[14,35] did not improve in the reperfusion group relative to the control group. This observation raises the possibility that the more rapid fall of S-T segment elevation may be attributed to hemorrhage and accelerated cell necrosis rather than to myocardial salvage. This does not exclude the possibility that the more rapid S-T normalization may correlate with a return of mechanical function at a much later time after reperfusion. However, since S-T elevation has been used as an index of the extent of myocardial injury,[8,36–42] our results suggest caution in the use of accelerated normalization of the S-T elevation as an indicator of reduction of infarct size.

In conclusion, our study has not shown reperfusion in the pig to be of benefit in the presence of acute myocardial infarction with occlusion times of 1 hour. Extensive intramyocardial hemorrhage and failure to witness improvement of ventricular wall motion after reperfusion was coupled with a significant decrease of S-T segment elevation. Neither mannitol nor general anesthesia reduced the severity of hemorrhage. Because hemorrhagic necrosis has also been noted in man in routine revascularization procedures in which patent grafts are found,[7] additional measures may be necessary to reduce temporary occlusion time or otherwise improve vascular integrity during revascularization surgery.

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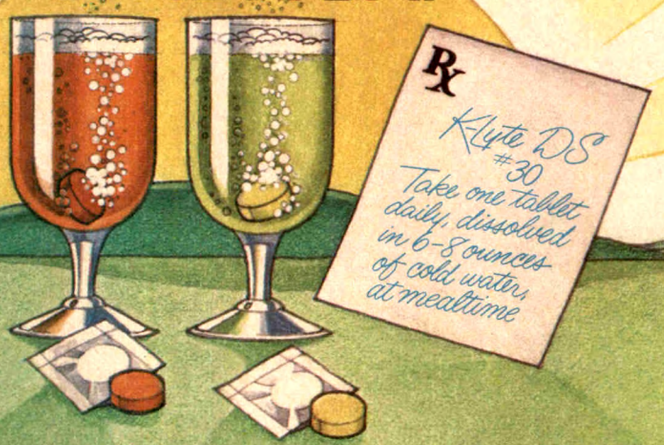

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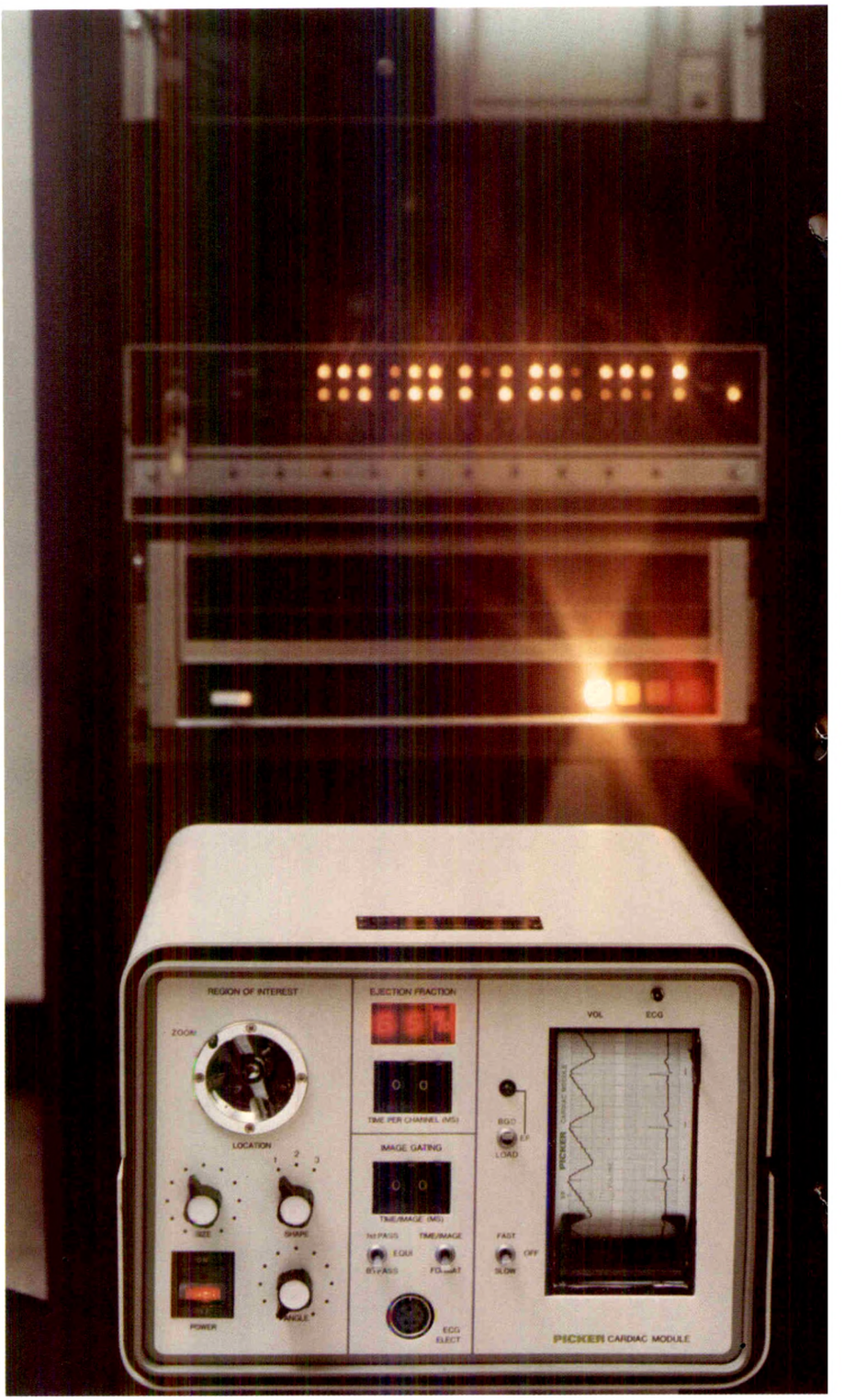

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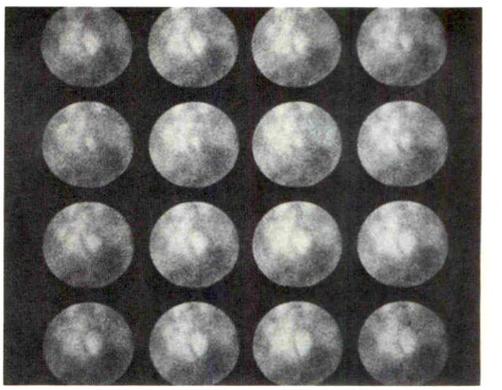

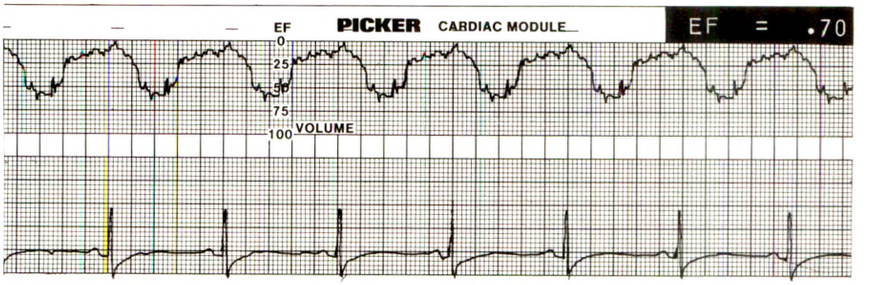

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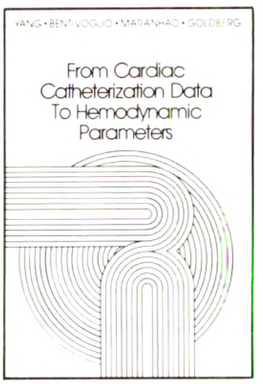

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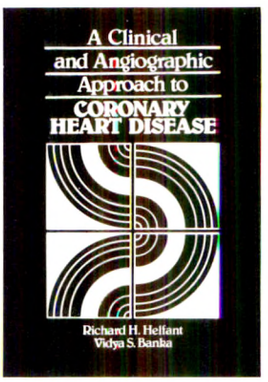

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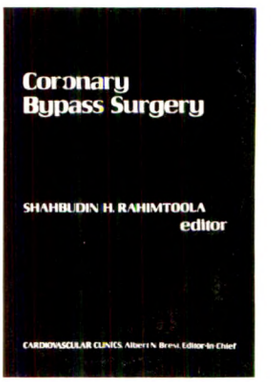

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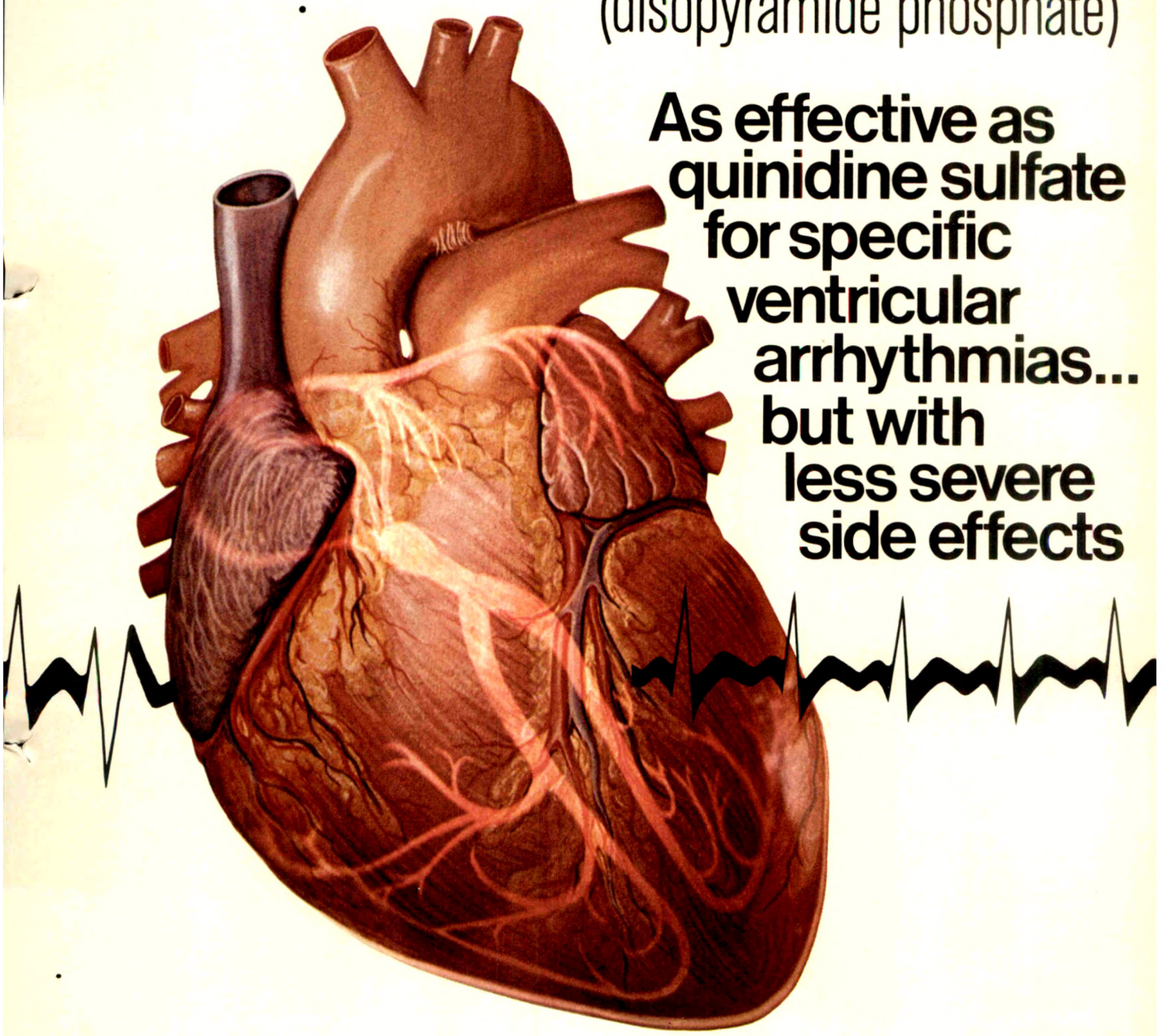

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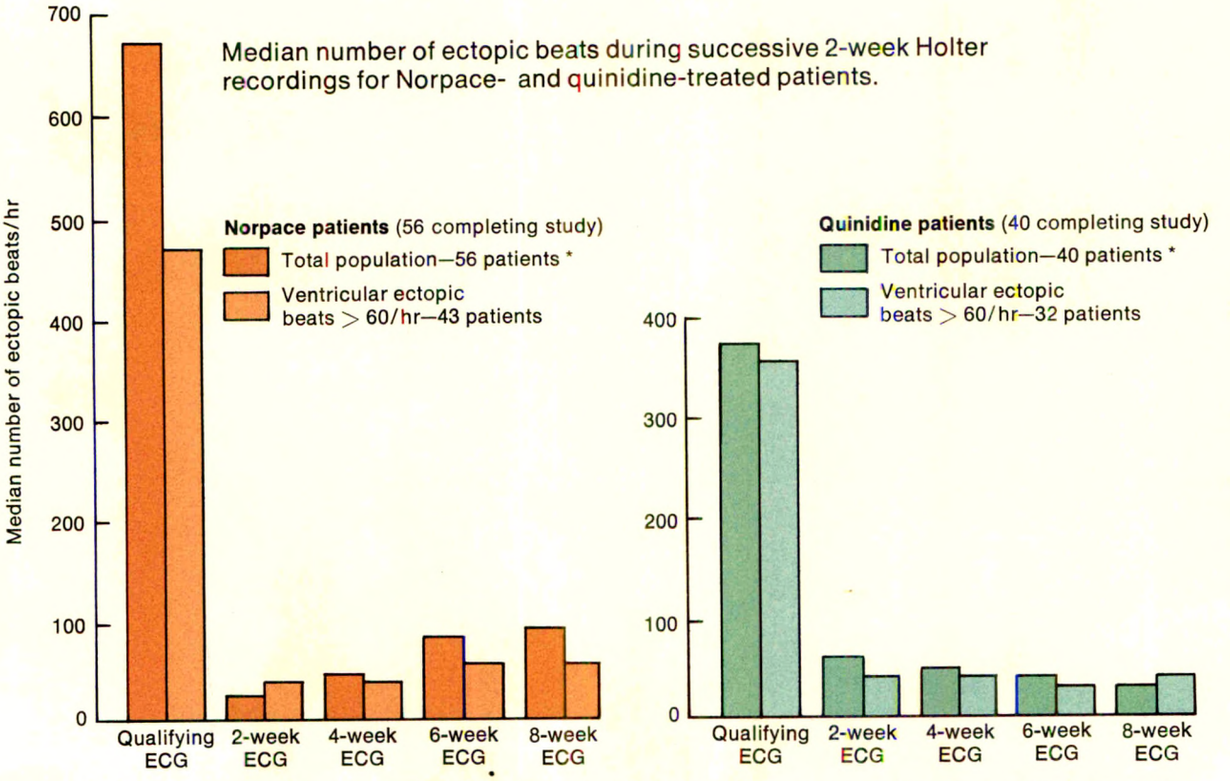

* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

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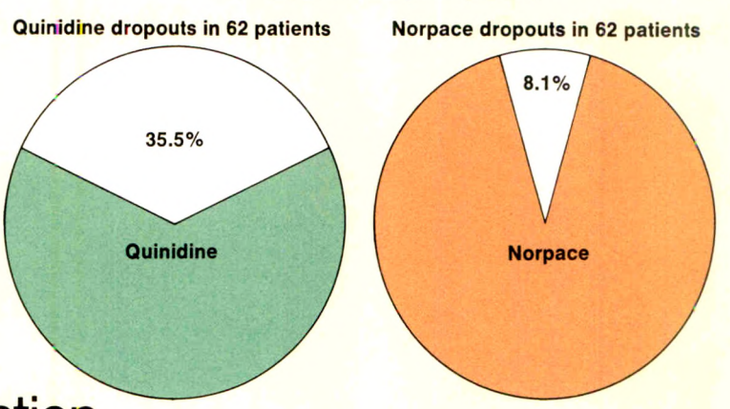
effective by extensive Holter monitoring

with less severe side effects

Significantly fewer dropouts with Norpace

(disopyramide phosphate)

The entire study population was analyzed for side effects. The side effects experienced by Norpace patients were usually mild and mainly anticholinergic, including: dry mouth, urinary hesitancy, constipation, blurred vision. The anticholinergic side effects were generally transient. Adverse reactions with quinidine were more serious and affected a greater number of patients. The most common symptoms were: severe diarrhea; gastrointestinal symptoms including cramps, nausea and vomiting; dizziness; fever; and rash.



Dosage and administration

Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose.

Recommended dosage regimen

Patient type	Loading dose	Maintenance dose
Adult	300 mg	150 mg q 6 h
Adults of smaller stature; or with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation	200 mg	100 mg q 6 h
Adults with severe renal insufficiency C_{cr} less than 40 ml/min	200 mg	100 mg given approximately every half-life (see Note below)

Note: Since Norpace is excreted in the urine, renal insufficiency appreciably extends the half-life of the drug. The chart below provides guidelines to the appropriate Norpace dosage in such patients.

Norpace dosage interval adjustment for patients with renal insufficiency

Creatinine clearance (ml/min)	40-15	15-5	5-1
Approximate maintenance-dosing interval	q 10 h	q 20 h	q 30 h

Norpace plasma half-life may also be prolonged in patients with significant liver disease.

Please see next page for a brief summary of prescribing information.

SEARLE

Norpace®
(disopyramide phosphate)

as effective as quinidine sulfate for specific ventricular arrhythmias...with less severe side effects

Before prescribing Norpace, please consult complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia, atrial arrhythmias or arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed on rare occasions, primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless it is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may cause cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency, dysuria. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *Central Nervous System:* nervousness, depression, insomnia, impotence, dizziness, general fatigue/muscle weakness, headache, malaise, and rarely, reversible acute psychosis. *Cardiovascular:* edema/weight gain, cardiac conduction disturbances, shortness of breath, syncope, chest pain, hypotension. *Dermatologic:* generalized rash/dermatoses.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose. The recommended initial dosage schedule for adults is a single loading dose of 300 mg, followed by 150 mg every six hours.

For patients of small stature, or for those with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation, a loading dose of 200 mg is recommended, followed by 100 mg every six hours.

For patients with severe renal insufficiency lower doses are recommended. See complete prescribing information for details.

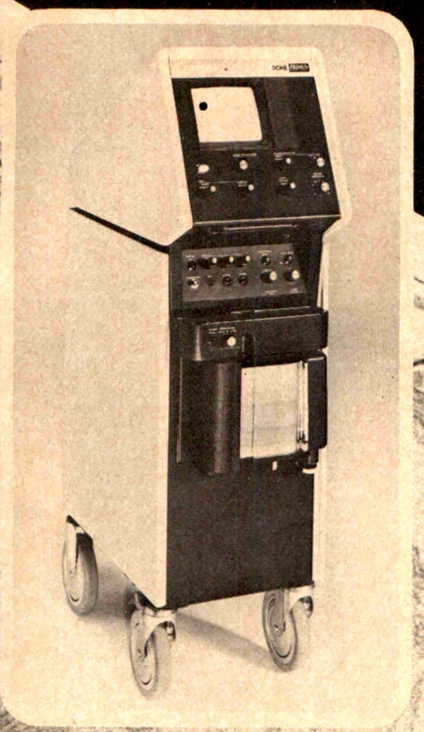
Overdosage: No specific antidote for Norpace has been identified; treatment of overdosage should be supportive. Overdosage might be expected to produce excessive widening of the QRS complex, worsening of congestive heart failure, hypotension, varying kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects might also be observed. The electrocardiogram should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given as required. In vitro studies have demonstrated good dialyzability for disopyramide.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

SEARLE

Searle Laboratories
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

7N2



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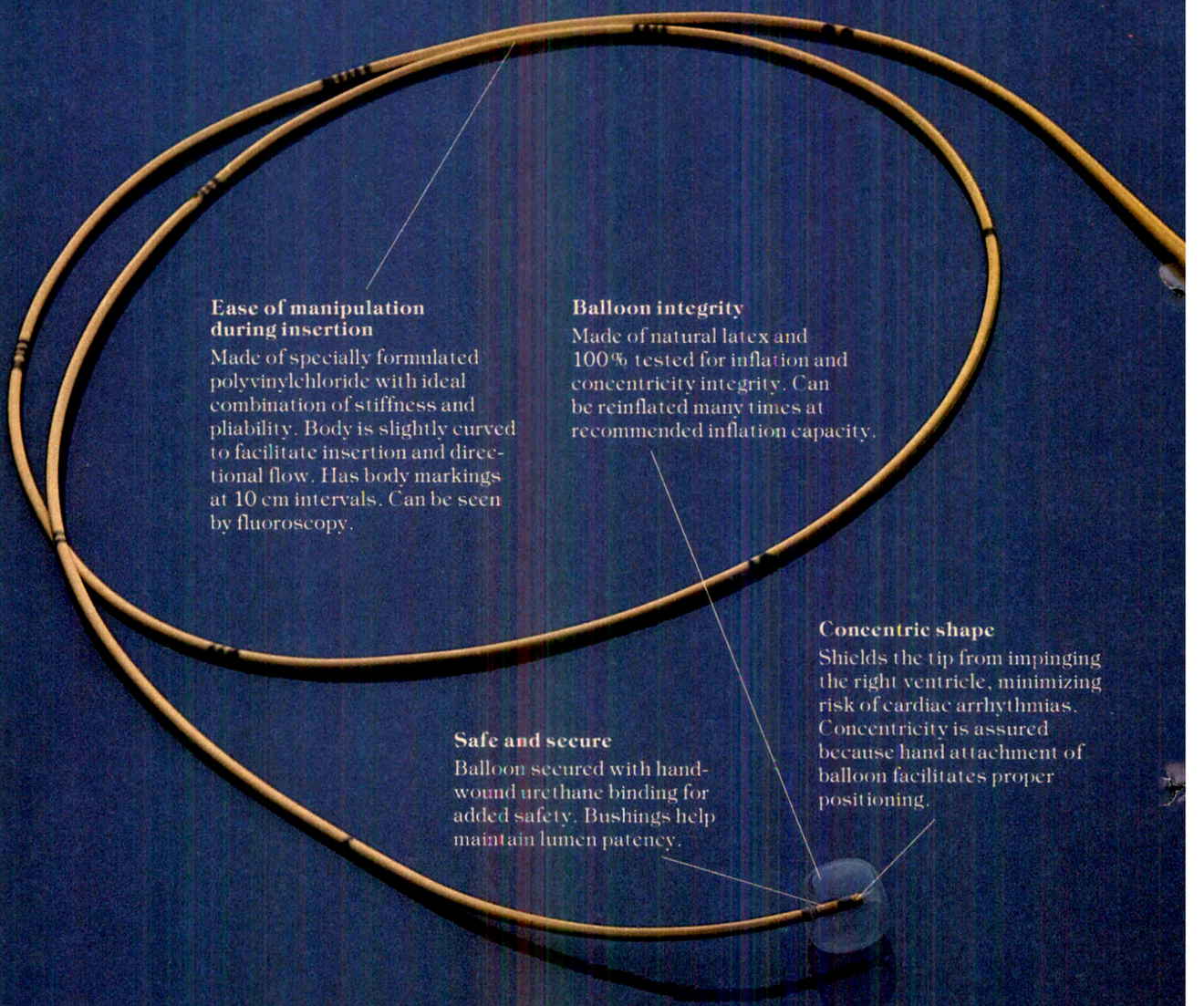
What to look for in the



Ease of manipulation during insertion
Made of specially formulated polyvinylchloride with ideal combination of stiffness and pliability. Body is slightly curved to facilitate insertion and directional flow. Has body markings at 10 cm intervals. Can be seen by fluoroscopy.

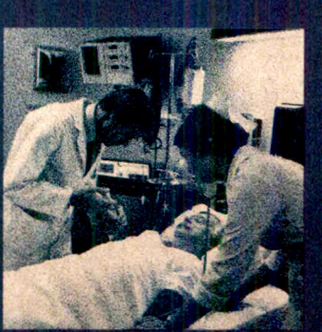
Balloon integrity
Made of natural latex and 100% tested for inflation and concentricity integrity. Can be reinflated many times at recommended inflation capacity.

Concentric shape
Shields the tip from impinging the right ventricle, minimizing risk of cardiac arrhythmias. Concentricity is assured because hand attachment of balloon facilitates proper positioning.

Safe and secure
Balloon secured with hand-wound urethane binding for added safety. Bushings help maintain lumen patency.

These are the features that have helped make the Edwards' SWAN-GANZ Catheter from Edwards Laboratories the most widely used in the world. In fact, of all open heart medical teaching centers in the United States, 85% of them routinely use the SWAN-GANZ Catheter for hemodynamic monitoring.

The reasons? More clinical experience (over one-half million inserted), hundreds of published papers in the medical literature, unsurpassed manufacturing quality (15 separate quality control checks), meticulous hand-



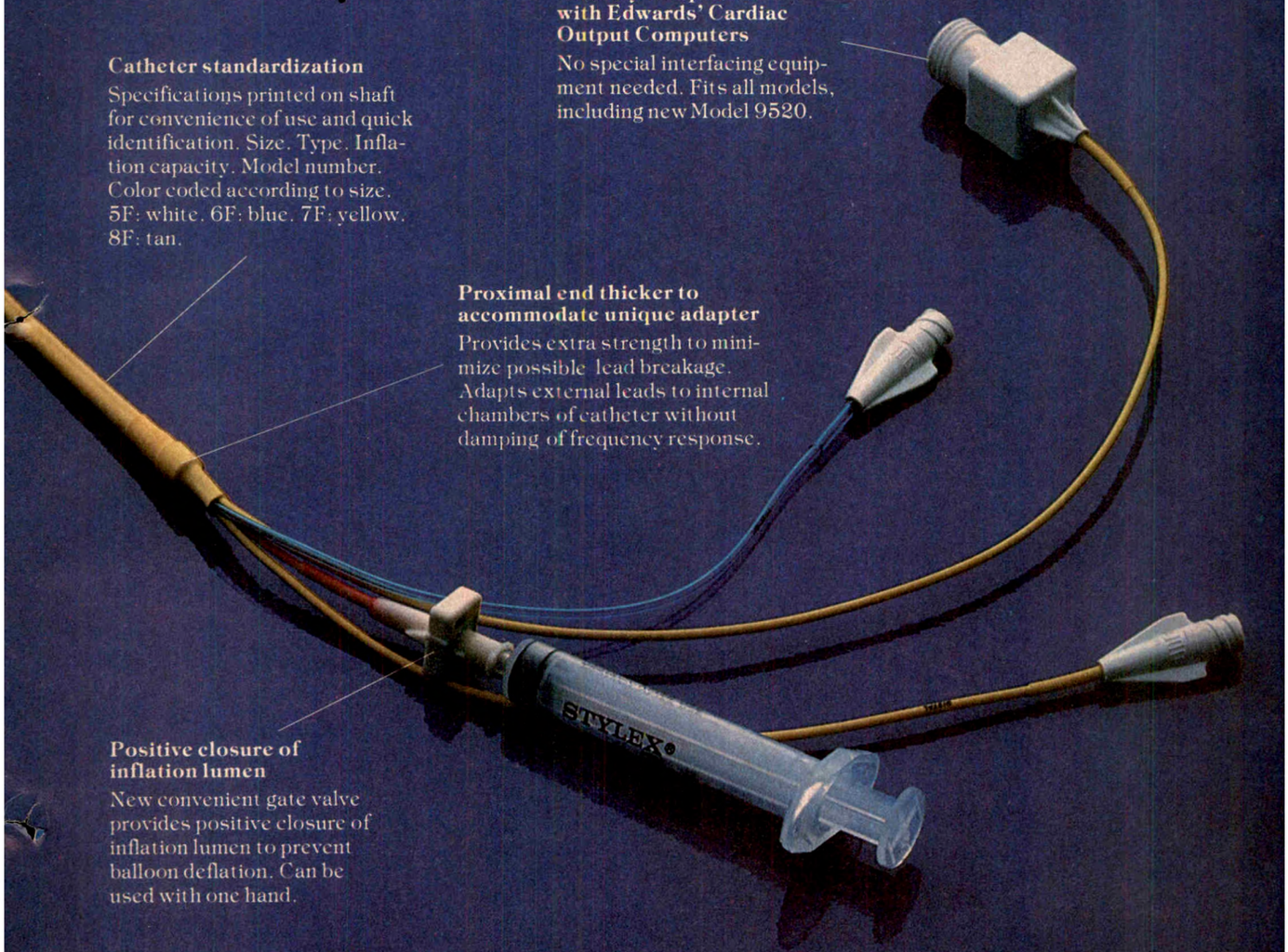
SWAN-GANZ is a registered trademark, Edwards Laboratories.

SWAN-GANZ® Catheter.

Directly compatible with Edwards' Cardiac Output Computers
No special interfacing equipment needed. Fits all models, including new Model 9520.

Catheter standardization
Specifications printed on shaft for convenience of use and quick identification. Size. Type. Inflation capacity. Model number. Color coded according to size. 5F: white. 6F: blue. 7F: yellow. 8F: tan.

Proximal end thicker to accommodate unique adapter
Provides extra strength to minimize possible lead breakage. Adapts external leads to internal chambers of catheter without damping of frequency response.



Positive closure of inflation lumen
New convenient gate valve provides positive closure of inflation lumen to prevent balloon deflation. Can be used with one hand.

wound construction, 100% testing, wide selection of catheter types/sizes, and support by a company dedicated to excellence in cardiovascular devices.

A complete description of SWAN-GANZ Catheters, details on insertion, placement and complications are described in journal reprints and technical data available from Edwards.

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Look for quality. Look to Edwards.

InterLith-RP
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RATE PROGRAMMABLE
C-MOS Model 252
Intermedics Inc.
FREEPORT, TEXAS
InterLith-RP
RATE PROGRAMMABLE
C-MOS Model 251
Intermedics Inc.
FREEPORT, TEXAS

InterLith™-RP.

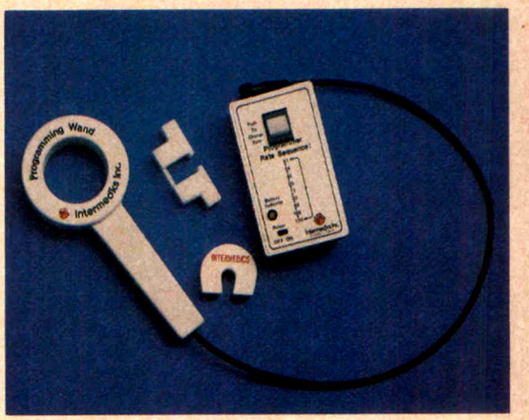
The pacemaker with a fail-safe rate programming design.

It took Intermedics to combine the most straightforward, uncomplicated rate programming system in the industry with the proven reliability of c-mos circuitry. Utilizing the superior longevity of a lithium power cell, Intermedics now offers you one of the smallest, lightest, most comfortable programmable pacemakers available...the InterLith-RP.

This pacemaker, unlike others on the market, utilizes circuitry that has been uniquely designed to avoid accidental reprogramming. This fail-safe feature requires the occurrence of two simultaneous electrical events; first, the magnetic reed switch must be closed and secondly, the programmer must be activated in immediate proximity to the pacemaker. The nine programmable rates are 51, 55, 60, 65, 72, 80, 90, 103 and 120 BPM. The rate is incremented from one value to the next by simply depressing the programming button.

A triumph of design, the InterLith-RP is hermetically sealed in tissue-compatible interference-resistant 316L stainless steel and measures only 6.0 cm × 4.6 cm × 1.5 cm (bipolar unit measures 6.3 cm in height), enabling a smaller incision resulting in a more cosmetic pocket. All edges are smoothly rounded for greatest patient comfort.

A lithium cell, plus low current drain under load, give the InterLith-RP a potential longevity in excess of 12 years*; like all other Intermedics pacemakers, the InterLith-RP is backed by a replacement credit agreement. Its universal connector readily accepts Intermedics' leads as well as most manufacturers' leads without adapters, making it an excellent choice when a replacement pulse generator is needed. InterLith-RP. The better programmable pacemaker.



For the location of your nearest Intermedics representative, or for additional information about our products, call toll-free 1-800-231-2330. In Texas, call collect 1-713-233-8611.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541

*Based on 72 BPM, 500 OHM load and 100% pacing.

InterLith is a trademark of Intermedics, Inc.

Note: The InterLith RP is currently being clinically evaluated.

See the InterLith RP at the American College of Cardiology Convention, March 6-9, Anaheim, California. Intermedics' Island booth #28.

Intermedics Pulse Generators

INDICATIONS FOR USE Pacemakers may be used in any application where asynchronous or demand ventricular pacing is indicated. These include congenital or acquired complete heart block which may be continuous or intermittent in nature, various types of sinus node dysfunction, WPW syndrome, carotid sinus hypersensitivity, drug induced bradycardia, and various ventricular arrhythmias.

The above list is not intended to be complete. The indications for pacing are increasing as the devices become more sophisticated and as methods for patient management become more widely understood.

PRECAUTIONS Implanted cardiac pacemakers have a finite service life and a relatively wide variability in service life. Factors affecting service life include the initial capacity of the battery and the shelf storage time of the manufactured pulse generator. Once implanted the anticipated service life of the generator is modified by variations in electrode system resistances, stimulation rate, and the percentage of time during which the pacemaker is inhibited. The current drain on the battery when inhibited is less than one-third of that when pacing with a typical lead installation. Other factors contributing to wide variability in service life are random electronic component failures.

All sensing pulse generators are inherently susceptible to magnetic electrical and electromagnetic fields. While design features are incorporated to minimize this susceptibility, an extraneous signal of sufficient strength and with characteristics which mimic normal cardiac activity can influence their operation. Additionally, certain environmental sources can couple sufficient energy into a cardiac pacemaker system to damage the pulse generator. Specifically, the implanting physician and the patient should be warned about the following:

(1) Electrocautery–Surgical use of electrocautery may cause temporary inhibition of the pulse generator. Additionally, pulse generator damage is possible if sufficient energy is coupled into it. Use of electrocautery within 4-5 centimeters of the implanted pacemaker can cause a direct coupling of RF energy through the lead and electrode to the cardiac muscle, producing burns or possible ventricular fibrillation.

Continuous monitoring of blood pressure and pulse should be instituted in all procedures where the use of electrocautery is contemplated. The ground plate of the electrocautery system should be placed in a manner to minimize current flow through the pacing system. A specific example is a TUR; during this procedure, the ground plate should be placed low on the buttocks or strapped to the thigh.

(2) Diathermy–A pacemaker patient should not receive this form of therapy. Very intense fields of microwave energy are involved and reactions of all sensing pulse generators are unpredictable. Total or virtually complete inhibition of the pacing circuitry is possible; however, no damage will result to the circuitry during the exposure.

(3) Microwave Ovens–Ovens, both in the home and in commercial use, in good condition and used as intended, will not affect the InterLith. Any microwave appliance which does not exceed federal guidelines of 0.5 milliwatts/cm² leakage at a point 2.5 cm. from the appliance will not affect the InterLith. However, appliances have been discovered which emit radiation in excess of 200 times these guidelines. The possibility of interference from such defective appliances does exist. The pulse generator will not be damaged by such exposure.

(4) Defibrillation–All implanted unipolar pulse generators regardless of manufacturer, can be damaged by cardiac defibrillation. Additionally, the presence of an implanted pacemaker system can increase the amount of cardiac muscle damage which results from defibrillation.

(5) Home Electrical and Gasoline Powered Appliances–Certain electrical and gasoline powered appliances can cause inhibition of an implanted cardiac pacemaker system. Pacemaker patients should be warned about the possibilities of pulse generator inhibition from some electric razors, most notably the rotary types, hand-held electric drills, power saws, and other appliances containing brush motors.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. The patient diagnosis and prognosis may indicate the type of pacemaker therapy used by the physician.

Body rejection phenomenon have been reported from the use of implanted cardiac pacemakers. These include local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism and cardiac tamponade.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541

Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) **80 mg**

Peritrate®
(pentaerythritol tetranitrate) **40 mg**

Peritrate®
(pentaerythritol tetranitrate) **20 mg**

Peritrate®
(pentaerythritol tetranitrate) **10 mg**

CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).

Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).

Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

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Division,
Warner-Lambert Company
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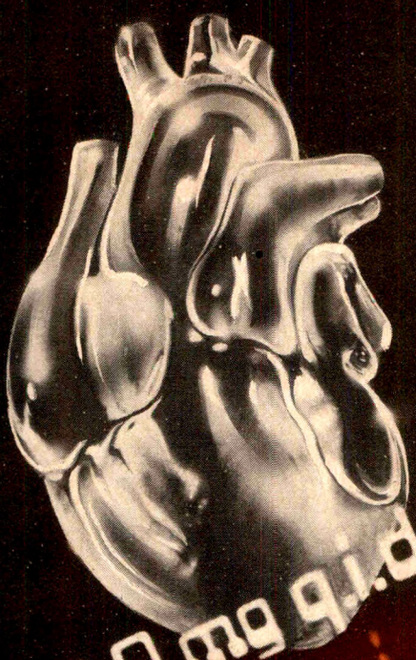

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Maximum Peritrate Dosage Simply and Conveniently

Peritrate® 40mg (pentaerythritol tetranitrate) Tablets q.i.d.

In many angina* patients, response to Peritrate is optimum when dosage is titrated to its maximum

The simple aim of Peritrate prophylaxis* is to maintain adequate nitrate levels in the body so that fewer "breakthrough" angina attacks occur. To achieve this goal, many patients require maximum dosage. Peritrate 40 mg tablets q.i.d. or Peritrate® SA Sustained Action 80 mg b.i.d. Whichever form of Peritrate you choose, be sure you use it optimally. You can expect side effects to be few.

*This drug has been evaluated as possibly effective for this indication.
See brief summary.

PE GP-74

40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.
40 mg q.i.d.

160 mg/day

WHAT TO LOOK FOR IN A CATHETER INTRODUCER SET

This is the UMI Sterile Percutaneous Catheter Introducer, available in sizes 4F to 9F. Using it, you can introduce balloon "floating" catheters, closed-end catheters, or electrode probes with great ease, thereby minimizing trauma to the patient. It is carefully thought out in design and engineering, and manufactured to our high quality standards.

Here are its main features:

1. CLOSE FIT. Each component is matched with precision to its neighbor. They move freely but firmly in contact with each other.

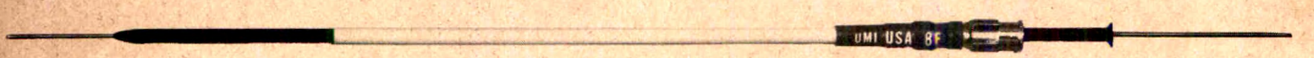
2. THE SHEATH IS TAPERED. For greater ease of introduction, the distal tip is tapered for a closer fit with the dilator. This is an exclusive UMI feature.

3. THE SHEATH IS THIN YET STRONG. Its wall is only .007" thick. Yet there is less chance it will "accordion" passing through tissue. Both it and the dilator are made of special Teflon.®

4. THE DILATOR'S DISTAL TAPER is uniform and gradual, meeting the guide wire closely for ease of introduction.

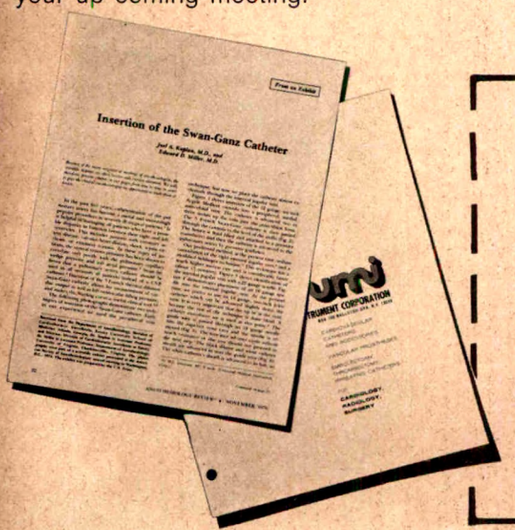
5. THE DILATOR'S FLARE is pronounced — so that it will not enter the sheath.

6. THE GUIDE WIRE is stainless steel, manufactured to close tolerances to assure uniformity.



Although we are a small, young company, UMI already produces catheters and catheter accessories in a great number of sizes and configurations. We will also custom-make to your specifications and needs. To learn more about what we can do for you, please send for a recent reprint from *Anesthesiology Review* and our current catalog — and see us at your up-coming meeting.

See us at our booth at the American College of Cardiology Convention in Anaheim. Please stop by and get acquainted.



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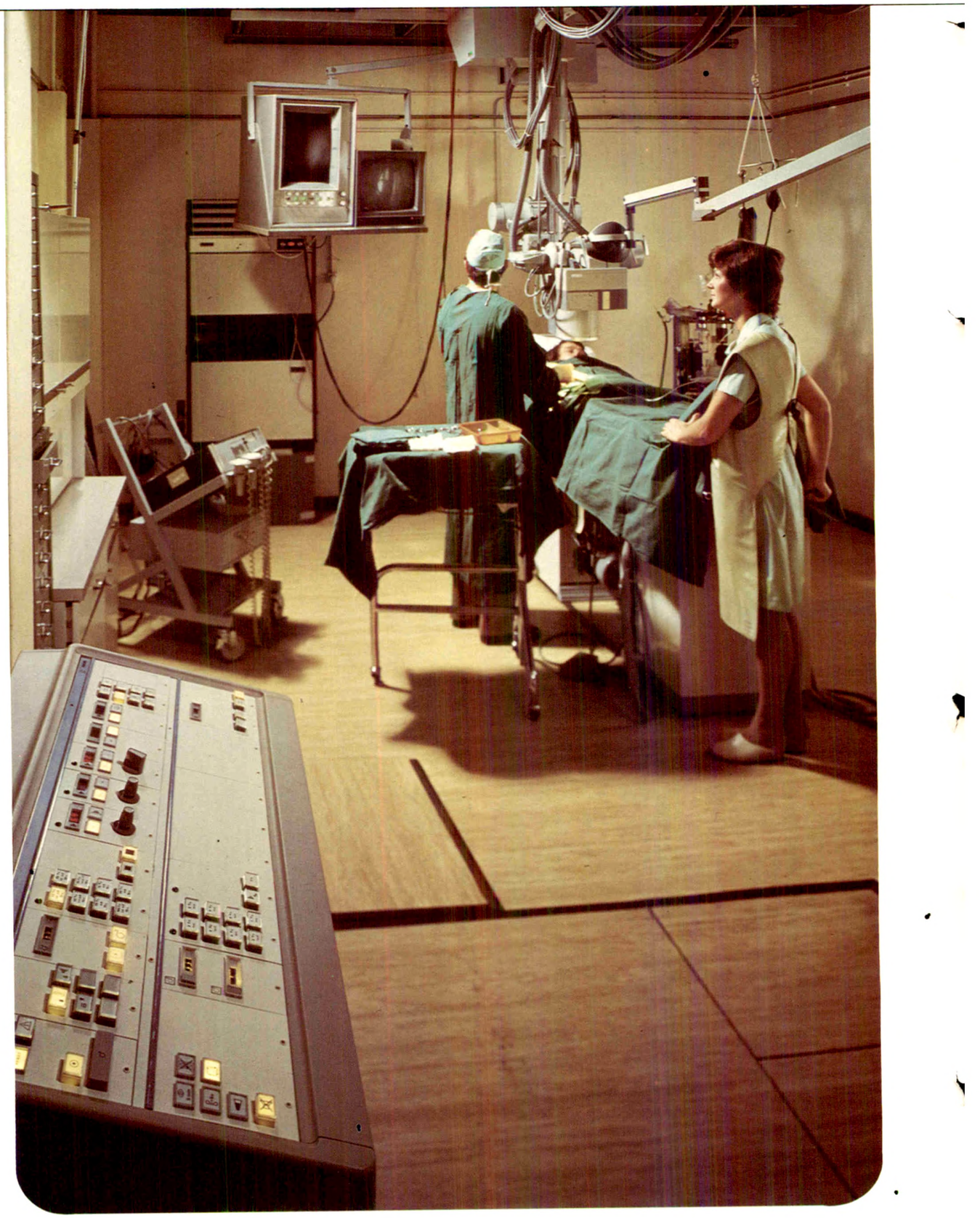
PHILIPS **Optimus** M200:

the ultimate clinical application of computer technology



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Consider computer technology completely dedicated to cardiovascular diagnostics...micro-circuitry that thinks and operates in your language according to your parameters and your procedure needs. Consider technology advanced to a degree that guarantees the perfect exposure for every run on every patient, regardless of age, size or weight. *This* is the OPTIMUS.

Full automation makes such accuracy simple for you. A range of programs covering every examination technique is built into the generator at installation. You select the medical parameters for each program. For examination, simply turn on the generator and press one button for the program you want. The OPTIMUS does the rest.

Patient Measuring Shots: Your Instant Preview
Automatically (in 5 milliseconds), the OPTIMUS measures the absorption characteristics of the patient and then the computer selects the exact factors for an ideal exposure. Factors are selected in discrete mA/kV steps. Your technique is always the highest mA and the lowest kV.

In a fraction of a second, all other technical parameters are calculated and set by the generator. You're insured perfect results before the cine run starts. The measuring shots can be engaged at any time to determine optimum technique for any projection.

Measuring shots drastically reduce the radiation dose required by less automated systems to determine technique factors. In the time equivalent to one cine frame, you know exactly what the results will be.

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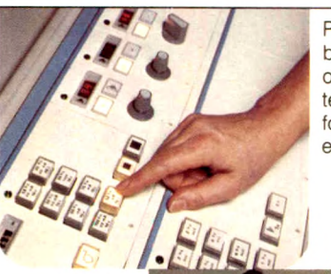

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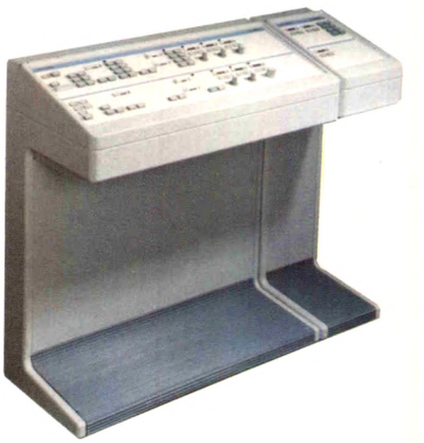

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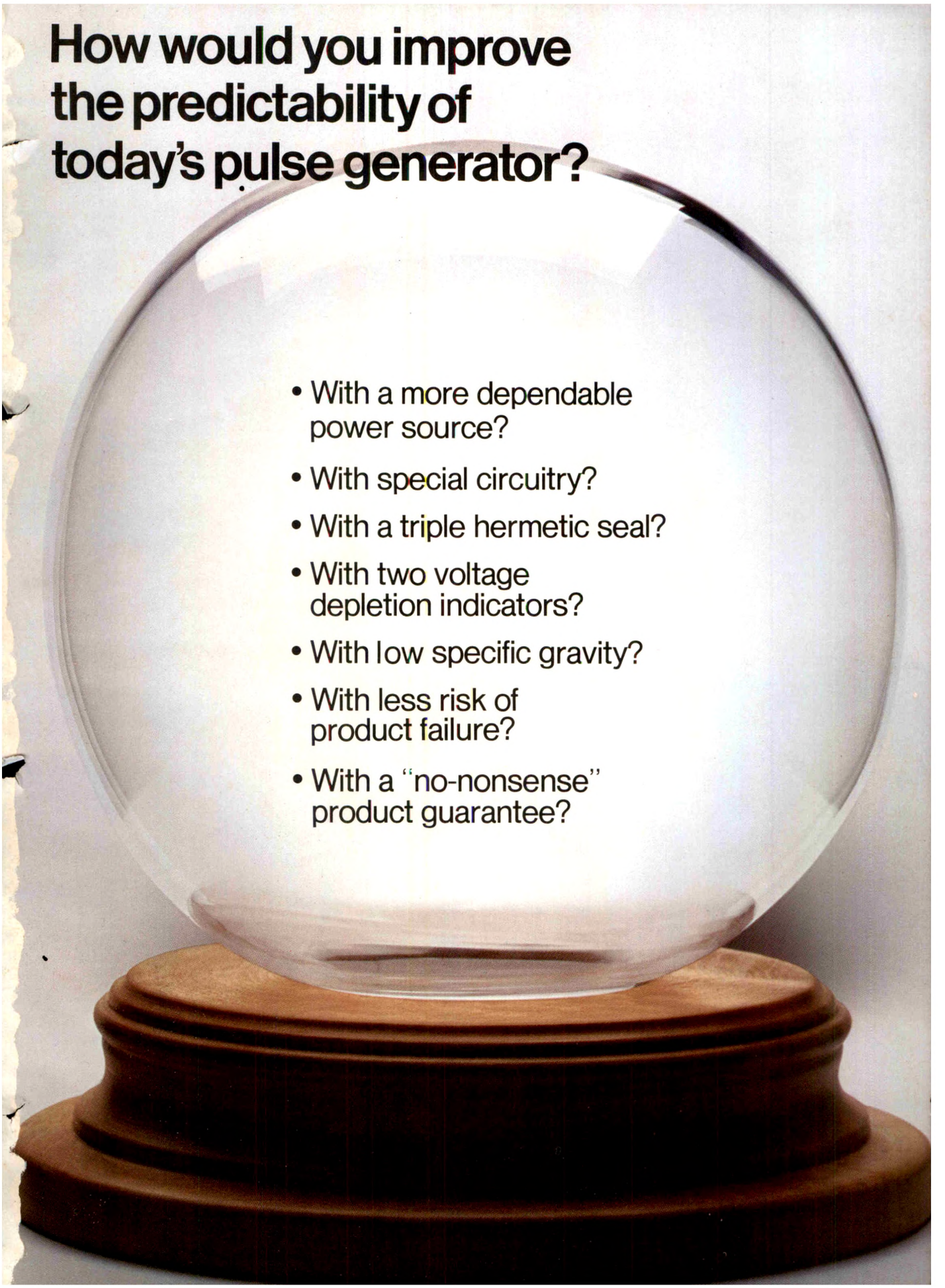

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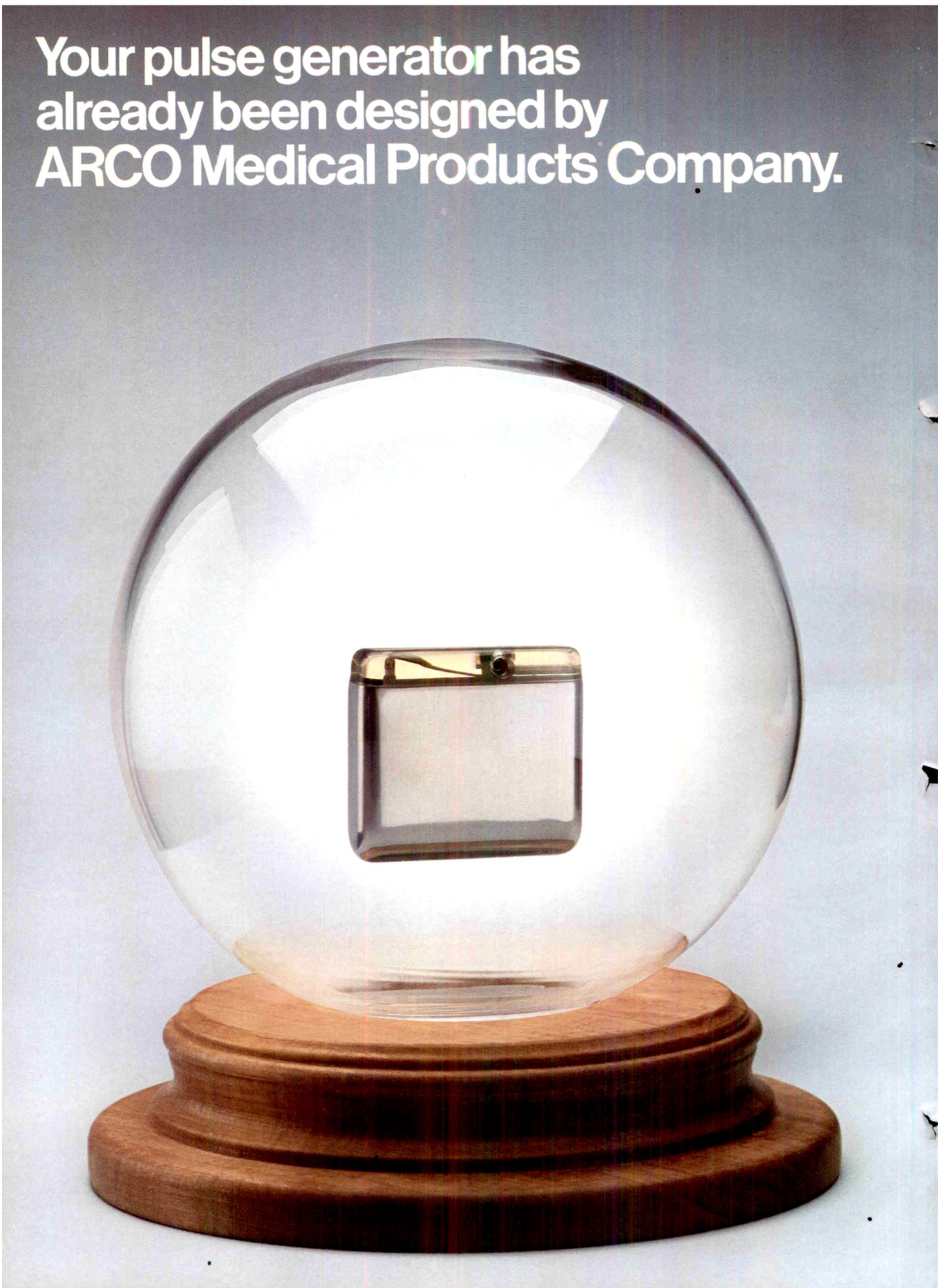

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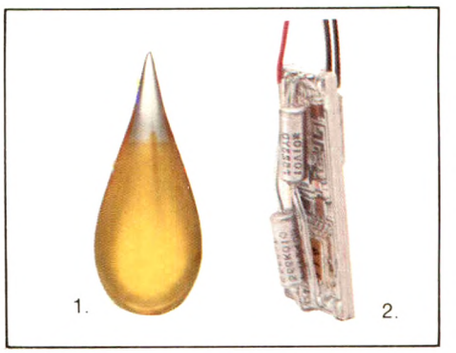

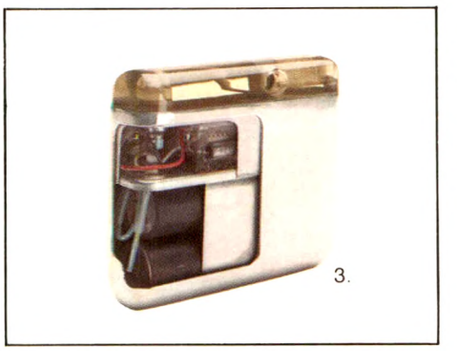

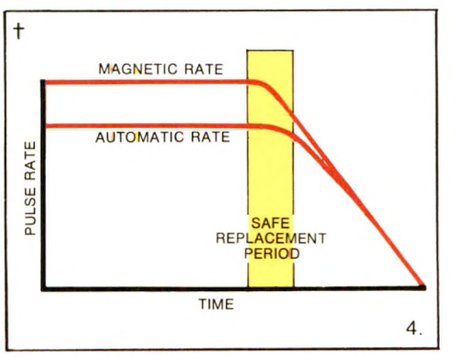

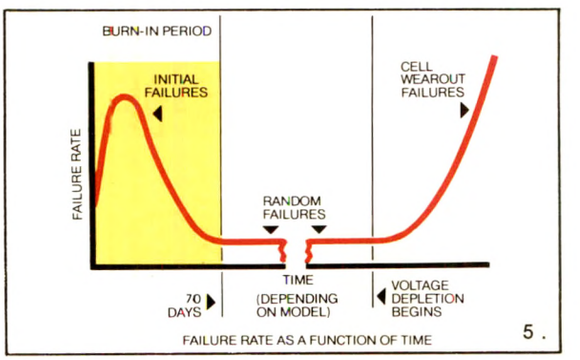

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Noninvasive Assessment of Coronary Stenoses By Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilatation

I. Physiologic Basis and Experimental Validation

K. LANCE GOULD, MD, FACC

Seattle, Washington

This study was undertaken to establish the basic hemodynamic conditions necessary to cause abnormalities in external myocardial perfusion images of thallium-201 and technetium-99M–labeled particles as a result of defined coronary stenoses ranging from mild to severe narrowing. Twenty dogs underwent long-term instrumentation with a flow transducer and adjustable constrictor on the left circumflex coronary artery. Catheters were implanted in the aortic root and distal left circumflex coronary artery to measure pressure loss across the stenosis and in the pulmonary artery and left atrium for the injection of drugs or radionuclides, or both. All data were obtained in intact unsedated trained animals. The results from 145 images obtained at rest, during exercise or after coronary vasodilators in dogs with mild to severe coronary stenoses demonstrate the following: (1) The ratio of maximal flow in a normal to stenotic coronary artery must be at least 2:1 before defects appear in the myocardial perfusion image of thallium-201. (2) A diagnostic technique that utilizes a maximal stimulus for increasing coronary flow and an imaging agent that is distributed to the myocardium in linear proportion to coronary flow at flow rates up to 4 or 5 times resting levels will be the most sensitive method for detecting mild coronary stenoses; a diagnostic technique utilizing a submaximal stimulus for coronary flow or an imaging agent whose distribution is not proportional to flow at high flow rates will be least sensitive. (3) Myocardial perfusion imaging during coronary vasodilatation induced with intravenously administered dipyridamole is a better method for identifying moderate coronary stenoses than perfusion imaging during exercise stress in experimental animals. (4) The effect of intravenously administered dipyridamole on the coronary circulation can be closely regulated by adjusting the dose rate of infusion and can be instantaneously reversed with intravenous administration of aminophylline, a dipyridamole antagonist; dipyridamole infusion does not increase myocardial oxygen demands as much as exercise and does not invoke myocardial ischemia as a diagnostic end point. This stimulus may therefore be more readily controlled than exercise stress and is not subject to the effects on treadmill testing of motivation, chronic lung disease, peripheral vascular disease or musculoskeletal impairment.

From the Veterans Administration Hospital and The Department of Medicine, University of Washington, Seattle, Washington. This work was supported by Veterans Administration MRIS Project 3217, Seattle, Washington Washington Heart Association grant 63-2749, Seattle, Washington and by from the National Institutes of Health, Grant HL 18492-01 Bethesda Maryland. Manuscript received May 11, 1977; revised August 22, 1977, accepted September 1, 1977.

Address for reprints: K. Lance Gould, MD, Veterans Administration Hospital, 4435 Beacon Avenue, South, Seattle, Washington 98108.

Myocardial imaging of thallium-201 injected at rest and during exercise stress is an important technique in the evaluation of coronary disease. However, the number of falsely negative results in patients with significant coronary disease documented with coronary arteriography ranges from 19 to 39 percent in several large clinical studies.[1–8] Although myocardial thallium imaging is quite useful when results are positive, it is not currently adequate for use as a diagnostic screening test in lieu of coronary arteriography because of the high number of false negative results.

There are several complex reasons for false negative thallium studies, including limitations of imaging hardware and geometry,[1,9] the time at which images are obtained after thallium injection as related to redistribution of this agent with disappearance of defects,[10] the presence of balanced coronary lesions which reduce perfusion equally and therefore produce no relative perfusion defect,[11] the effects of drugs, such as digitalis, propranolol and diuretic agents on thallium uptake,[12] the technique of exercise stress[3] and the problem of overlying myocardial structures or lung.[1] The problem is further complicated by variability in interpretation of coronary arteriograms and the difficulty of relating arteriographic appearance of stenoses to their hemodynamic effects. Although these factors have been recognized as procedurally important in current medical reports, there is no published description of the more basic physiologic principles or conditions that determine whether a specific coronary stenosis will cause a defect in thallium perfusion images at rest or at high coronary flow rates during stress.

The purpose of this report is (1) to describe the hemodynamic conditions necessary to produce abnormal myocardial perfusion images caused by experimental coronary stenoses of defined hydraulic severity in chronically instrumented intact awake active animals using thallium-201 and technetium-99M–labeled macroaggregated albumin particles, and (2) to validate experimentally a new noninvasive method for assessing the hemodynamic severity of coronary stenoses based on these physiologic principles and utilizing pharmacologic coronary vasodilatation as a potentially more effective and controlled stress than exercise.

Methods

Surgical Preparation

Anesthesia in 20 male dogs weighing 22 to 28 kg was induced with intravenously administered sodium thiopental, and anesthesia was maintained with methoxyflurane anaesthetic gas delivered through a Heidbrink vaporizing bottle with supplemental oxygen delivered into the intake of a Harvard volume respirator. Through a sterile left thoracotomy the left circumflex coronary artery was dissected free and a snugly fitting electromagnetic (Zapeda, Seattle, Washington) or Doppler flow transducer was placed around the proximal circumflex coronary artery; 2 to 3 mm distally a saline-filled inflatable constrictor was tied into place. In the distal main circumflex artery prior to major branches a small tapered Tigon catheter was inserted into the lumen and sutured into place with 6-0 silk passed through a cuff on the catheter. Similar catheters were implanted into the root of the aorta, the left atrium and the pulmonary artery. All catheters and wires were tunneled under the skin and exited individually 2 cm apart through 2 mm stab wounds in the skin over the back. The chest was closed in four layers with evacuation of the pneumothorax through a chest tube that was then removed. Dogs were treated with dipyridamole (Persantine®), 75 mg, and aspirin, 900 mg, for 2 days preoperatively and for 10 days postoperatively to prevent formation of platelet clots on the catheters in the postoperative period. After 10 days these drugs were discontinued without ill effects or malfunction of the catheters. Catheters were flushed daily, filled with heparin and stoppered with obturators made from 19 gauge needles cut off at the tip and filled with Silastic.®

Implanted Instruments

Doppler flow velocity transducers were made from 3.5 × 4.5 mm LTZ-2 lead titanate-zirconate piezo ceramic soldered to stainless steel coaxial cable (AS633-ISS, 38 AWG, Cooner Sales Company, California) and mounted in cast epoxy with air backing and coated with Parylene C by vapor phase deposition (Nova Tran Corporation, California) to insulate the transducer against body fluids. The coated wire was pulled through Silastic tubing which was then filled with self-leveling RTV 734 Silastic as a protective coating against mechanical abrasion. A continuous wave-directional Doppler flowmeter (L and M Electronics, Daly City, California) was used to measure instantaneous mean cross-sectional flow velocity at 8 to 9 megahertz after being tuned to maximal signal to noise ratio. Each transducer was calibrated on shrink tubing (3.54 mm outer diameter × 3.0 mm inner diameter) through which dog blood flowed; volume flow, F, was measured with a graduated cylinder and stopwatch. Mean cross-sectional velocity, V, was calculated from the equation $V = F/A$, where A was the cross-sectional area of the lumen of the shrink tubing. The voltage output of the Doppler flowmeter was measured with a digital voltmeter over a range of flow from zero to 156 cm/sec and the calibration factor calculated as cm/sec per volt output. The L and M Doppler flowmeter with these transducers was linear from zero velocity up to the maximum measured of 156 cm/sec (600 cc/min through a tube with an inner diameter of 3 mm). The calibration factor determined in vitro before implantation was also the same as that obtained by postmortem perfusion of the left circumflex artery with blood after experiments were completed and was the same on large as on small tubes. Electromagnetic flow transducers were calibrated in vitro by perfusion with blood using a graduated cylinder and stop watch. In those experiments in which electromagnetic transducers were used, zero baseline was determined by occluding the coronary artery with the coronary constrictor at the beginning and each of each experiment.

Catheters for implantation were made from Tigon micro bore tubing (0.025 inch inner diameter × 0.04 inch outer diameter [0.064 × 0.102 cm], Norton Plastics Company, Los Angeles, California). Tubing was dipped in oil heated to 140°C, drawn to a taper, cooled on dry ice and cut to fit snugly over a 25 gauge needle. A 2 to 3 cm long section of this small tapered tubing was welded with cyclohexanone to a 2.5 inch (6.35 cm) section of larger tubing, 0.04 inch inner diameter × 0.15 inch outer diameter (0.102 × 0.381 cm). A 4 inch (10.2 cm) 25 gauge needle was inserted through the tubings such that the tip projected 1 mm beyond the tip of the tapered small catheter. A slanted 1 mm long Tigon cuff was welded onto the small tubing near the tip. At operation the needle and catheter were thrust through the arterial wall with a twisting motion up to the cuff and secured to the adventitia of the artery with a 6-0 silk suture previously passed through the Tigon cuff. The needle was then withdrawn, the tubing flushed with saline solution, clamped with a rubber shod hemostat, wiped dry with a gauze sponge and welded with cyclohexanone to a 60 cm section of the larger tubing for exiting from the chest. After 1 minute's drying time, this joint was strong enough to withstand aortic pressure. Blood was then aspirated to remove any residual cyclohexanone and the catheter was flushed and filled with heparin. There was no bleeding site with this technique because there was no arteriotomy or exit hole in the artery.

Coronary constrictors were made by wrapping a 2.5 cm long section of Silastic tubing (0.058 × 0.077 inch [0.148 × 0.196 cm]) around a 4 mm diameter steel rod and bonding a stiff

radiolucent backing (strips of X-ray film) over it with self leveling Silastic RTV 734. One end of the tubing was sealed with RTV and the other end glued to a 50 cm long thick-walled silastic actuator tubing (0.030 × 0.095 inch [0.076 × 0.241 cm]) for exiting from the chest. The constrictor was evacuated under high vacuum and filled with saline solution before each experiment.

Experimental Procedure

Dogs were trained to lie quietly on a table and experiments were begun 2 weeks postoperatively when resting heart rates had decreased to 60 to 80 beats/min and resting mean aortic pressure was 65 to 85 mm Hg. Aortic and coronary pressures distal to the constrictor were measured with Bio-Tec BT-70 pressure transducers or differential pressures across the stenosis using a differential pressure gauge (National Semiconductor Coporation, Santa Clara, California, part no. Lx1701D), or both. Needle obturators, stopcocks and plastic parts were all filled by immersion under sterile saline solution in a vacuum chamber that was then evacuated under high vacuum in order to remove micro air bubbles and maximize frequency response. Sterile saline solution debubbled in the vacuum chamber was also used for flushing connections between catheters and pressure gauges. For each experiment pressure calibrations were recorded with 100 mm Hg pressure applied to the aortic, coronary and differential transducers at the beginning, middle and end of each study.

Protocol: Recordings were made on an Electronics for Medicine DR-12 with a direct writer. After a 10 minute rest period in a darkened room with no one moving about the laboratory, flow and pressure calibrations and baseline control recordings were made of the electrocardiogram, coronary flow velocity and aortic, coronary and differential pressures. The coronary constrictor was then expanded with saline solution under pressures up to 2,000 mm Hg (40 psi) depending on the severity of stenosis desired. The expansion pressure was held constant at the chosen level by a water-sealed ball valve in line with an automatic pressure regulator attached to an air pressure source. During the first 30 minutes after inflation of the constrictor, the stenosis tended to drift and become less severe despite constant inflation pressure. This early drift in stenosis was most likely due to squeezing fluid out of the tissues that grew between the arterial wall and the constrictor. After 30 minutes of adjustment the stenosis remained stable at whatever level of severity was selected. A dose of 0.5 cc of papaverine in a concentration of 2.0 mg/cc in debubbled saline solution was then injected through the coronary catheter to produce transient hyperemia while mean pressures and flow were recorded. Three minutes later when flow had returned to control levels dipyridamole was injected intravenously to produce more sustained maximal coronary flow. At peak response to dipyridamole, which occurred 4 minutes after the intravenous injection, thallium-201 was injected intravenously or technetium-99m–labeled macroaggregated albumin (MAA) or albumin microspheres were injected into the left atrium. In exercise experiments dogs ran on an enclosed treadmill instead of receiving dipyridamole to increase coronary flow. A radionuclide imaging agent was then injected as the dog ran at the 9th minute of a 10 minute run at 12.8 km/hour on a 10° incline.

Dogs were then externally imaged with an Ohio Nuclear Series 100 gamma camera in left lateral, 45° left anterior oblique and the same left anterior oblique view but with the gamma camera tilted 10° so that the camera faced cephalad, slightly "looking" up the long axis of the left ventricle. Thallium-201 was imaged at 80 keV with a full width half maximal window, and technetium-99m was imaged at 140 keV, also with a full width half maximal window. In each ease 300,000 count images were obtained with a low sensitivity high resolution collimator. Myocardial images were obtained 1 week apart to allow residual activity from the experiment of the previous week to decay to levels undetectable with external imaging. Thallium-201 cannot be imaged satisfactorily in the presence of technetium-99m because the 140 keV gamma emission of technetium causes a secondary lead (of the collimator) gamma emission of 80 keV, the same energy as that of the thallium-201 gamma emission. Technetium-99m images were therefore also obtained on this once weekly imaging schedule.

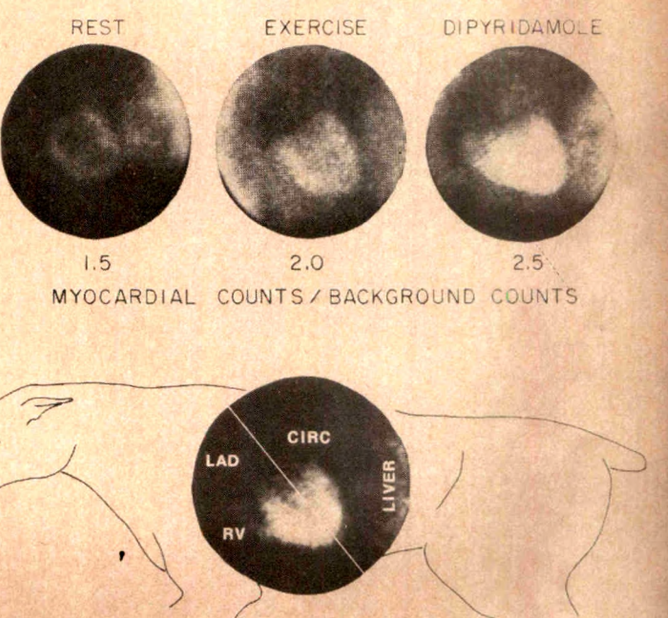

FIGURE 1. Myocardial perfusion images of a dog after intravenous injection of thallium-201 at rest, during treadmill exercise and during coronary vasodilatation induced with intravenously administered dipyridamole. All images were processed identically with 5 percent background subtraction. The orientation of myocardial images in relation to canine anatomy is shown with the distribution of the left anterior descending (LAD) and left circumflex (CIRC) coronary arteries. Relative myocardial uptake of thallium-201 and the quality of the images, expressed as myocardial:background activity ratios (before background subtraction), were greatest after dipyridamole infusion. RV = right ventricle.

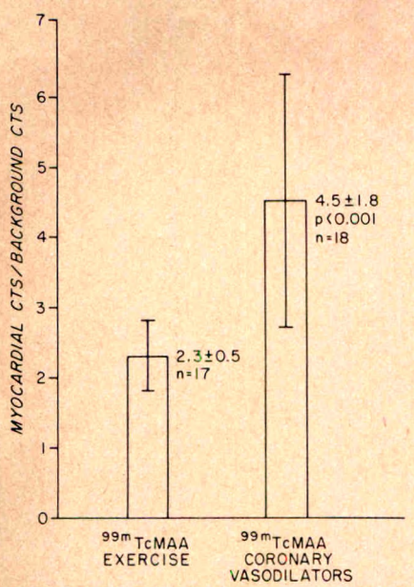

FIGURE 2. Relative myocardial activity (CTS) expressed as myocardial: background ratios of perfusion images obtained after left atrial injection of technetium-99m-labeled macroaggregated albumin (^{99m}TcMAA) during treadmill exercise and during coronary vasodilatation induced with dipyridamole. n = number of images; p = probability. Values expressed as mean ± 1 standard deviation.

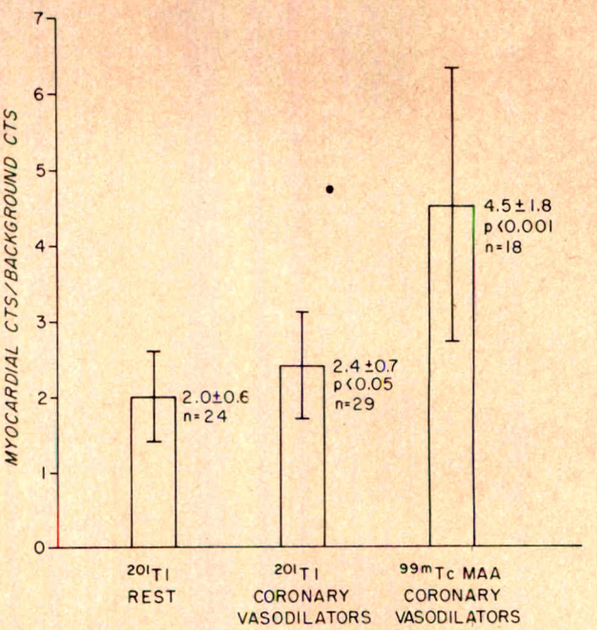

FIGURE 3. Relative myocardial activity (CTS) expressed as myocardial: background ratios of perfusion images obtained after intravenous injection of thallium-201 (^{201}Tl) and left atrial injection of technetium-99m–labeled macroaggregated albumin (^{99m}TcMAA) during comparable coronary vasodilatation with intravenously administered dipyridamole. Values indicate mean ± 1 standard deviation.

Data Analysis

Recordings of differential pressure and flow were manually traced on a Grafpen GP-2 ultrasonic digitizing tablet and processed in a PDP-8 computer. The coronary flow velocity and pressure difference between the aorta and the distal main circumflex artery (pressure gradient) due to a stenosis were digitized into 100 pressure points and a corresponding 100 velocity points for each cardiac cycle and were digitally filtered using the method of central differences. The digital filter was equivalent to a low pass filter flat to 15 hertz and having linear rolloff from 15 to 30 hertz (−40 decibels down at 30 hertz) and introduced no phase shift. During each cardiac cycle the pressure gradient and flow velocity were correlated by a quadratic equation having the general form $\Delta P = FV + SV^2$, where ΔP is the pressure loss in mm Hg, V is the coronary flow velocity in cm/sec, F is the coefficient of pressure loss due to viscous friction and S is the coefficient of pressure loss due to flow separation or localized turbulence downstream from the stenosis (and Gould KL, unpublished data).[13] For single heart cycles the constants F and S were determined that best fit this general equation to the experimental data by computer utilizing a general purpose curve-fitting algorithm previously described.[14] Three to six heart cycles for flow ranging from resting control to peak flow during coronary vasodilation were analyzed for each stenosis. Computer printouts of experimental data for each cardiac cycle were obtained with pressure gradient plotted on the vertical axis and flow velocity on the horizontal axis.

All radionuclide imaging data were collected and stored in dedicated computer systems consisting of Nova II and 1220 with 24K and 32K core memory, (Medical Data Systems, Ann Arbor, Michigan), 128 × 128 matrix display, dual magnetic disc drives and tape storage systems. Original scintiphotographs of in vivo perfusion images were used for interpretation. Computer-reproduced images with 5 percent background subtraction were used for illustrations and all images shown for comparison purposes in this article were processed identically with identical 5 percent background subtractions so that artifactual or apparent abnormalities were not created by computer reproduction. Localized profiles of each image were located on memory oscilloscopic display to determine the ratio of myocardial to background activity. Each dog had control images taken at rest and after coronary vasodilators or exercise, or both, without stenoses of the coronary arteries as well as with stenoses. The average number of images per dog was 7.5.

Results

Figure 1: This figure shows examples of identically processed myocardial perfusion images of a normal dog after intravenous injection of thallium-201 at rest, during treadmill exercise and after intravenous injection of dipyridamole. The uptake of thallium-201 by the myocardium relative to lung, that is, the myocardial to background ratio, determined from original measurements of activity without background subtraction, reflects the quality of the image and relative myocardial uptake. In this example dipyridamole produced a greater increase in coronary flow and thallium-201 uptake than treadmill exercise. Subsequent figures show mean myocardial to background ratios of images obtained under various conditions using intravenously administered thallium-201 and technetium-99m–labeled macroaggregated albumin.

Figure 2: This figure shows the relative degree of uptake of technetium-99m macroaggregated albumin, an entirely flow-distributed agent, during exercise and during pharmacologic coronary vasodilatation. The mean myocardial to background activity ratio during treadmill exercise was 2.3 ± 0.5 (mean ± standard deviation), which is considerably lower than the 4.5 ± 1.8 ($P < 0.001$) found during pharmacologic coronary vasodilatation. This observation indicates that

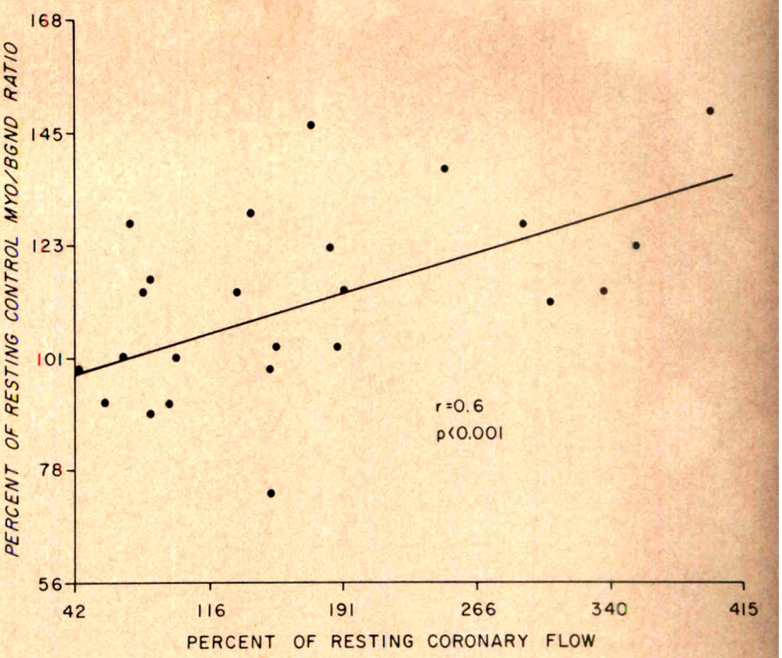

FIGURE 4. Relation between percent change in coronary flow from resting control values and percent change in relative myocardial activity expressed as myocardial: background (MYO/BGND) ratios of thallium-201 perfusion images. The relative myocardial uptake of thallium-201 failed to increase in proportion to increases in flow. Coronary flow was varied by using various intravenous doses of dipyridamole up to 0.6 mg/kg.

in experimental animals coronary vasodilators are a more effective stimulus for coronary flow than treadmill exercise.

Figure 3: This figure shows the effects of using an imaging agent, technetium-99m macroaggregated albumin, whose distribution is proportional to flow in contrast to thallium-201, whose uptake is not proportional to flow at high flow rates. For comparable flow stimuli using coronary vasodilators, the myocardial to background ratios of 4.5 ± 1.8 for technetium-99m macroaggregated albumin images were higher than the 2.7 ± 0.7 observed with thallium-201. This finding suggests that an imaging agent that is distributed in the myocardium in proportion to flow will result in better myocardial images than an imaging agent that is not taken up by the myocardium in proportion to flow at high flow levels of up to 4 or 5 times baseline levels.

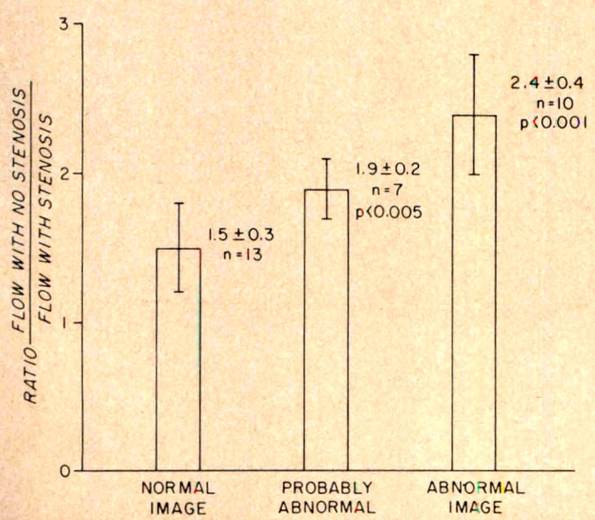

FIGURE 5. Ratio of maximal flow in the normal coronary artery to maximal flow in the stenotic coronary artery during coronary vasodilation in relation to myocardial images of thallium-201 injected after intravenous administration of dipyridamole. Values expressed as mean ± 1 standard deviation.

Figure 4: This figure shows that the percent change in myocardial to background ratios of thallium-201 did not increase proportionately with percent increase in coronary flow measured with a flowmeter. There was a poor correlation between thallium-201 uptake measured with external imaging and increase in coronary flow for flow levels up to 4 times resting levels ($r = 0.6$) with sufficient scatter to prevent estimation of changes in coronary flow from thallium uptake.

Figure 5: This figures shows the ratios of peak coronary flow after administration of a vasodilator in a normal coronary artery to the peak flow with a stenosis on the artery in relation to perfusion defects in thallium-201 images taken after infusion of dipyridamole. A 2:1 flow ratio indicates that during coronary vasodilation flow in the normal artery was twice as great as in the stenotic artery; a 1:1 flow ratio indicates no impairment of maximal flow. A flow differential between the normal and stenotic coronary artery of 2.4 ± 0.4 times was required to cause a definite defect in the thallium image.

Table I: This table shows pressure losses across stenoses and coronary pressures distal to the stenoses in relation to

TABLE I

Pressures with Thallium-201 Myocardial Images

Myocardial Image	ΔP (mm Hg)	Distal Coronary Pressure (mm Hg)
Normal (no. = 12)	25 ± 7	57 ± 15
Probably abnormal (no. = 7)	37 ± 9 $P < 0.025$	49 ± 16 NS
Abnormal (no. = 9)	45 ± 15 $P < 0.005$	37 ± 9 $P < 0.005$

ΔP = pressure losses across stenoses; NS = not significant; P = probability.

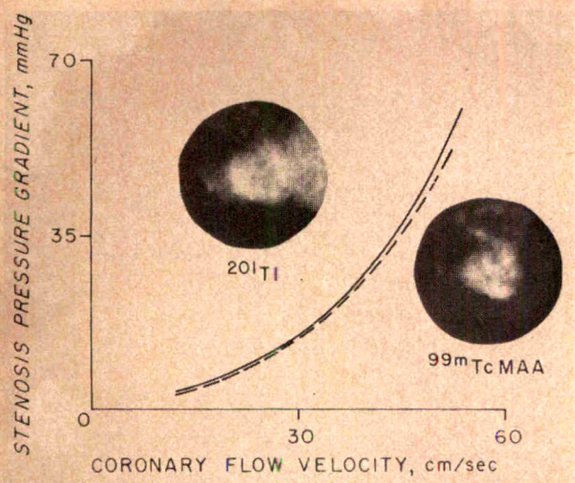

FIGURE 6. Graphic plot of the pressure gradient-flow velocity relation characterizing the hemodynamic severity of stenoses of the left circumflex coronary artery of a dog. A stenosis of defined hemodynamic severity was applied and a thallium ^{201}Tl perfusion image obtained during dipyridamole induced coronary vasodilatation. After completion of the study the stenosis was released. One week later, after all residual thallium activity had disappeared, a second stenosis of identical severity was applied and a perfusion image was obtained of technetium-99m macroaggregated albumin (^{99m}TcMAA) injected into the left atrium during comparable coronary vasodilatation. In this manner the relative sensitivity of different imaging procedures for detecting identical stenoses were tested. In this example with a moderate circumflex stenosis a perfusion image of thallium-201 injected during dipyridamole-induced coronary vasodilatation failed to demonstrate a defect **(upper left image and solid line).** However, with a hemodynamically identical stenosis a perfusion image of technetium-99m–labeled macroaggregated albumin injected into the left atrium during comparable coronary vasodilatation showed a mild but definite decrease in activity in the circumflex distribution **(right border of the lower right image and dashed line).** Left lateral views are shown.

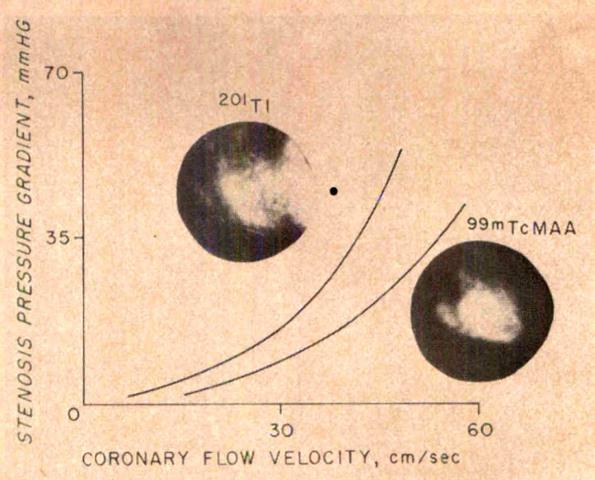

FIGURE 7. Hemodynamic characteristics of coronary stenoses producing comparable defects on thallium and technetium MAA perfusion images. There is a mild but definite decrease of activity in the circumflex distribution **(right border)** of the thallium (^{201}Tl) image **(upper left photograph** and **upper curve)** as well as the technetium-99m macroaggregated albumin (^{99m}TcMAA) image **(lower right photograph** and **lower curve).** The pressure gradient-flow velocity relation characterizing the hemodynamic severity of the stenosis causing the thallium defect is steeper than for the stenosis causing the defect on the technetium image. Thus, a more severe stenosis was required to produce a thallium than a technetium defect.

perfusion defects in thallium-201 myocardial images. Abnormal images were associated with stenosis gradients of 45 ± 15 mm Hg and distal coronary pressures of 37 ± 9 mm Hg at peak coronary vasodilatation when thallium-201 was injected. *P* values shown are in comparison with the normal images in which the stenoses were too mild for detection by myocardial imaging.

Figure 6: From an experimental point of view, the severity of a stenosis is best defined in terms of its pressure-flow characteristics, that is, the plotted or mathematical relation between the pressure gradient caused by a coronary stenosis and the flow velocity through the coronary artery[13,15,16] (and Gould KL, unpublished data). The pressure gradient due to a stenosis was related to coronary flow velocity according to a curved line (shown as an example in Fig. 6). For a fixed coronary stenosis, the pressure gradient increased as flow velocity increased in response to any stimulus, such as exercise or coronary vasodilators. With more severe stenosis the pressure gradient-flow velocity relation became steeper and more curved, moving upward and leftward on the graph. With less severe stenosis the relation moved downward and rightward. This method of defining the severity of the stenosis in hydraulic terms did not require knowledge or comparison of the geometry of the stenosis or size of the coronary artery because the effects of percent narrowing, absolute stenosis

TABLE II

Hemodynamic Changes with Abnormal Images

	Thallium-201	*P* Value	Technetium-99m Macroaggregated Albumin
Flow ratio*	2.4 ± 0.4 (no. = 10)	<0.025	1.9 ± 0.4 (no. = 13)
Pressure gradient (mm Hg)	45 ± 15 (no. = 9	NS	38 ± 6 (no. = 13)
Distal coronary pressure (mm Hg)	37 ± 9 (no. = 9)	<0.05	45 ± 8 (no. = 13)

* Ratio of flow with no stenosis to flow with stenosis.
NS = not significant; *P* = probability.

diameter, length and degree of streamlining all had a final common influence on pressure loss or flow velocity. Figure 6 illustrates two hemodynamically identical coronary stenoses imaged during dipyridamole-induced coronary vasodilatation using thallium-201 and subsequently using technetium-99m macroaggregated albumin. For a stenosis of this relatively moderate hydraulic severity, thallium-201 imaging failed to demonstrate a defect whereas technetium-99m macroaggregated albumin clearly showed decreased perfusion in the circumflex distribution (right border) of this left lateral view.

Figure 7: This figure shows that a stenosis that yielded a mild but definite circumflex defect with thallium-201 imaging during coronary vasodilatation was more severe hydraulically (upper curve) than a stenosis that yielded a comparable defect in a technetium-99m macroaggregated albumin image during comparable vasodilatation (lower curve).

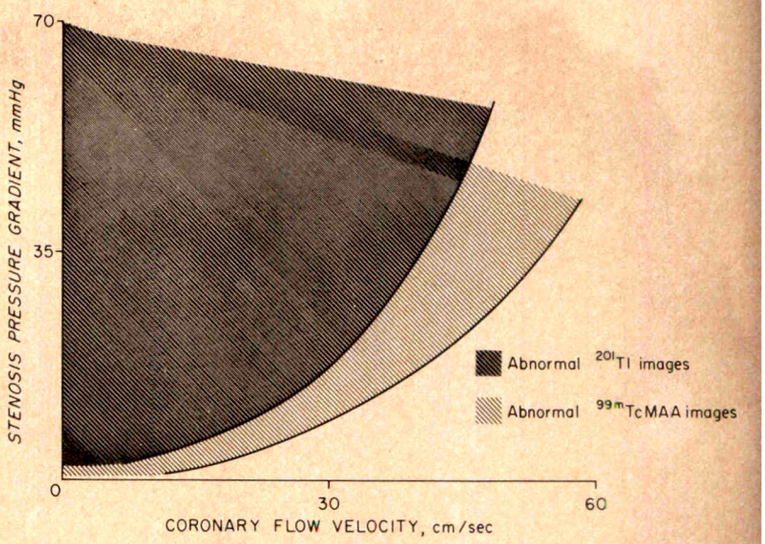

FIGURE 8. Composite pressure gradient-flow velocity curves of 24 coronary stenoses in relation to abnormal myocardial images using thallium-201 (^{201}Tl) and technetium-99m macroaggregrated albumin (^{99m}TcMAA). Less severe coronary stenoses were consistently detected with ^{99m}Tc technetium than with thallium images.

Figure 8: This figure shows the composite results of 24 coronary stenoses defined by similar pressure-flow curves in relation to abnormal myocardial images. In term of hydraulic curves, myocardial images using technetium-99m macroaggregated albumin identified milder stenoses than thallium-201.

Table II: This table compares the hemodynamic changes associated with abnormal thallium and technetium images. The ratio of maximal flow in an artery with no stenosis to maximal flow in an artery with a stenosis indicated the severity of flow impairment and relative flow maldistribution. Abnormal technetium-99m images were associated with significantly less severe flow abnormalities than abnormal thallium-201 images. Pressure losses or gradients across the stenoses and coronary pressures distal to the stenosis were also less severely affected, indicating that milder coronary stenoses were detected with technetium than with thallium. Thus, a method utilizing an imaging agent that was distributed in proportion to flow was more sensitive than an imaging agent that was not taken up in proportion to flow at high flow rates.

Figure 9: This figure illustrates one of three experiments in which there was an inadequate coronary vasodilatory stimulus for imaging the effects of coronary stenoses. In this example the two coronary stenoses were hemodynamically identical and were both imaged with thallium-201. For the image on the left associated with the solid curve, an inadequate dose of dipyridamole was used and no defect is apparent in the image. For the image on the right associated with the dashed curve an adequate dose of dipyridamole was used and a mild but definite abnormality developed in the distribution of the stenosed circumflex coronary artery.

Figure 10: This figure further illustrates this point using exercise as the "inadequate" stimulus. The stenoses in this example were hydraulically identical and both were imaged with thallium-201. In the left image the stimulus for increasing coronary flow was exercise stress and no perfusion defect developed. In the right image the stimulus was intravenously administered dipyridamole which clearly resulted in an abnormality in the distribution of the stenosed left circumflex artery. These findings indicate that a potent stimulus for coronary vasodilatation increased the sensitivity of an imaging method for assessing coronary stenoses over that of a less potent stimulus.

Figure 11: This shows the minimal dose of intravenously administered dipyridamole necessary to produce maximal or near maximal coronary vasodilatation in dogs. Maximal vasodilation was arbitrarily defined as the flow response after 10 seconds of occlusion in the absence of stenosis. Both the rate at which dipyridamole was infused and the absolute dose given were important determinants of the coronary flow response. Various intravenous dose infusion rates were tested to determine which dose rate would produce maximal or near

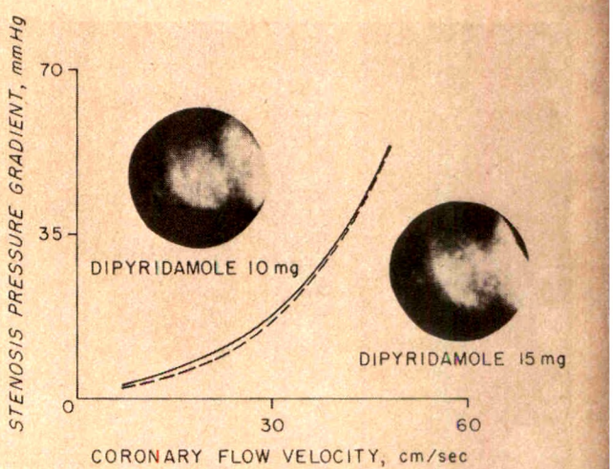

FIGURE 9. Effect of an inadequate stimulus for coronary vasodilatation on the sensitivity of thallium imaging for detecting coronary stenoses. The thallium image at **upper left** associated with the **solid line** failed to demonstrate a defect during submaximal coronary vasodilation. With a hemodynamically identical coronary stenosis **(dashed line)**, adequate coronary vasodilatation caused a mild but definite decrease of activity in the circumflex distribution **(right border)** of the thallium image at **lower right.**

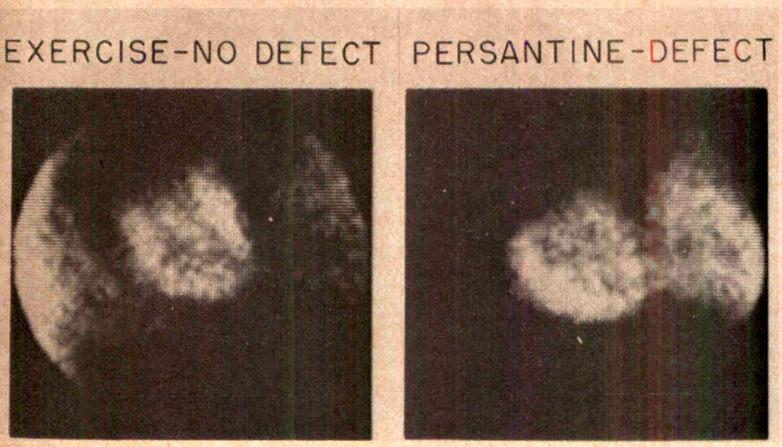

FIGURE 10. Myocardial perfusion images of thallium-201 injected during treadmill exercise **(left)** and during dipyridamole (Persantine)-induced coronary vasodilatation **(right)**. The circumflex arterial stenosis for the left image was hemodynamically identical to that for the right image with the same pressure gradient-flow velocity relation. No defect was present in the exercise thallium image **(left panel)**, whereas a definite decrease of activity occurred in the circumflex distribution **(right border)** of the dipyridamole thallium image **(right panel)**.

maximal coronary flow for 3 to 5 minutes, the time required for most thallium-201 to be taken up by the myocardium. At a dose rate of 0.142 mg/kg per min for 4 minutes coronary flow reached 95 percent of the peak flow response after 10 seconds of occlusion. The peak coronary response to dipyridamole occurred 5 minutes after the end of the 4 minute infusion and persisted for 3 to 5 minutes thereafter with this regimen. The response to a 10 mg bolus dose (average 0.4 mg/kg) and a 15 mg bolus injection (0.68 mg/kg) are also shown.

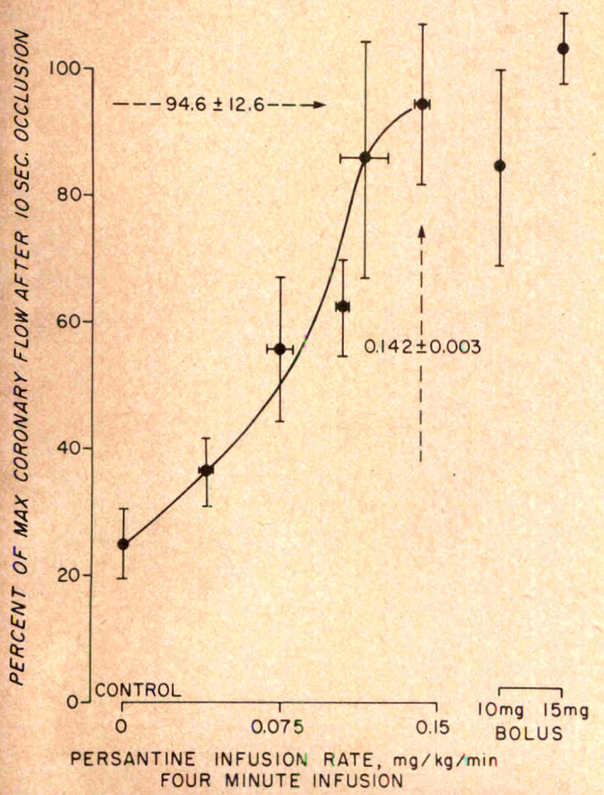

FIGURE 11. Response of coronary flow to various dose-rate intravenous infusions of intravenous dipyridamole (Persantine) in intact unsedated animals. The optimal dose rate for imaging purposes was 0.142 mg/kg per min for 4 minutes. Values indicate mean ± 1 standard deviation. MAX = maximal.

Discussion

External imaging of regional myocardial perfusion during pharmacologic coronary vasodilatation for the detection of coronary stenoses was initially reported by Gould et al. in experimental animals[17] and in man[11] and subsequently in a clinical series by Ritchie et al.[18] These studies demonstrated a physiologic basis for assessing the severity of coronary stenoses in terms of restricted coronary flow reserve and sharply separated normal subjects from patients with hemodynamically significant coronary disease. However, the method required coronary arteriography with intracoronary injection of contrast medium as the stimulus for coronary vasodilatation and intracoronary injection of technetium-99m macroaggregated albumin for imaging regional myocardial perfusion. The need for an invasive procedure limited the clinical applicability of the approach.

Horwitz et al.[19] described a pharmacologic stress test using the xenon-133 technique to measure coronary blood flow during infusion of isoproterenol. This method statistically separated a group of normal subjects from a group of patients with coronary disease. However, the patients with coronary disease had severe coronary lesions, and the sensitivity of the technique for more moderate lesions was not evaluated. In addition, the regional localization of abnormalities in myocardial perfusion could not be identified because, instead of a gamma camera, precordial counting probes were used to record total myocardial clearance curves. Yamazaki et al.[20] confirmed the use of contrast medium as well as intravenously administered dipyridamole to assess coronary flow reserve in stenotic coronary arteries of experimental animals. Cole et al.[21] recorded increased coronary flow velocity in patients with a catheter-tip Doppler velocity detector after the intracoronary injection of contrast medium. Bassan et al.[22] measured coronary sinus blood flow with a thermodilution catheter during coronary vasodilatation induced with intracoronary injection of contrast medium. This technique also statistically separated normal subjects from patients with coronary disease but there was sufficient overlap between the groups to render the results of limited diagnostic benefit in any individual patient:

Holman et al.[23] imaged xenon-133 clearance during coronary vasodilatation caused by intracoronary injection of contrast medium. Again, a normal group could be statistically separated from a group with coronary disease but the results were not specific enough for reliable diagnosis in individual cases.

More recently, noninvasive methods of myocardial imaging have become available, particularly those utilizing thallium-201. Strauss et al.[24] evaluated myocardial imaging of thallium-201 and potassium-43 injected during coronary vasodilatation induced with adenosine-5-carboxylate in order to identify subcritical coronary stenoses. The studies reported here, undertaken independently over the past 3 years, establish the physiologic requirements and validity of utilizing thallium-201 imaging during coronary vasodilatation induced with dipyridamole in order to identify coronary stenoses of hydraulically defined severity.

Treadmill exercise stress as a stimulus for coronary flow: Our results demonstrate two principal physiologic requirements of any method for assessing coronary flow reserve. The first is a potent stimulus for increasing coronary flow in order to maximize regional perfusion abnormalities that can then be imaged externally. Although exercise increases coronary flow, the relation between the level of exercise and the degree to which coronary flow increases is unclear. In our study dogs running on a treadmill at 12.8 km/hour for 10 minutes on a 10° incline increase coronary flow by 100 to 150 percent, a finding in agreement with previous reports.[25–28] This level of exercise is approximately equivalent to stage 6 or 7 of the Bruce protocol for maximal treadmill stress in man.[29] By analogy, such treadmill stress in man would therefore not be a satisfactory stimulus for coronary flow, which reportedly can increase 4 to 5 times resting levels after pharmacologic stimuli, which are more potent than treadmill stress.[30]

However, higher coronary flow levels have been reported during treadmill testing in dogs under certain conditions. Particularly well trained dogs[31] or dogs making the transition from rest to exercise[32] or pulling a loaded sled in a cross-country run may increase coronary flow by 4 or 5 times.[33] Thus, the point of maximal treadmill exercise in animals is not clearly defined and the relation of treadmill stress in dogs to treadmill stress in man is even more obscure. Dipyridamole injected intravenously during strenuous exercise stress causes considerable further coronary vasodilation and increase in coronary flow in dogs.[32] During treadmill stress in man coronary flow reportedly increases only modestly. Messer et al.[34] reported that during exercise stress the average increase in coronary flow ranged from 33 to 44 percent (average increase 39 percent), depending on the clinical diagnosis. This average was 139 percent of control resting values for all patients. Parker et al.[35] showed that coronary flow increased 77 percent over resting levels in eight normal subjects and 49 percent in seven patients with coronary disease. These figures are 177 percent and 149 percent, respectively, of control resting coronary flow values. Knoebel et al.[36] described increases of up to 100 percent in coronary flow during exercise with an average increase of 20 percent, or 129 percent of control levels in 12 patients. Holmberg et al.[37] described exercise coronary flow values averaging 252 percent of resting coronary flow or an increase of 152 percent in 10 patients. Methodologic limitations on the methods for measuring coronary flow subject all of these results to some question. Using the argon technique, which is reportedly accurate at high rates of coronary flow, Heiss et al.[38] reported coronary flow increases of 103 percent in trained and 213 percent (203 percent and 313 percent, respectively, of control resting values) in untrained subjects during exercise.

The effectiveness of exercise stress as a stimulus for coronary flow may also be limited by motivation of the subject, pulmonary or peripheral vascular disease and the effects on exercise performance of cardiac drugs such as propranolol and prior physical training. Conditioned athletes demonstrate significantly less increase in coronary flow for a given level of exercise than deconditioned subjects.[38] In the presence of coronary disease the development of myocardial ischemia during exercise may cause angina pectoris, which limits exercise to a sufficiently low level that the normal areas of myocardium are not stressed adequately and coronary flow does not increase enough to produce regional perfusion defects by external imaging.

Dipyridamole as stimulator of coronary flow: The specific type of coronary vasodilator does not appear to be of critical importance so long as it is selective for the coronary arteries, has insignificant systemic effects and has an effect for at least 3 minutes until thallium-201 is removed from the systemic circulation. Experimentally, contrast media, papaverine, adenosine triphosphate or nitroglycerin given by intracoronary injection in adequate doses or 10 seconds of occlusion provide a satisfactory stimulus for coronary vasodilatation. Coronary vasodilatation in the presence of a coronary stenosis results in an increased pressure gradient and a decrease in distal coronary pressure as coronary flow increases.[15,16,39–41] This increased pressure loss associated with increasing coronary flow through a stenosis is a basic fluid dynamic characteristic of an arterial narrowing[13,15,16,39,40] as shown by the pressure-flow relation in Figures 6 to 9. Thus, any potent coronary vasodilator has the potential of producing subendocardial hypoperfusion[27,41–48] by causing a reduction in distal coronary perfusion pressure despite an increase in epicardial coronary artery flow.

Intravenously administered dipyridamole was used in this study for several reasons: (1) It is a potent coronary vasodilator with few systemic effects; (2) it is the only selective coronary vasodilator that has been extensively used in man (in Europe) and for which the Food and Drug Administration has granted an Investigational New Drug permit in the United States for clinical studies; and (3) its pharmacologic effects on the coronary circulation can be completely blocked within a few seconds by the intravenous administration of aminophylline.[41,49–53] thereby permitting complete control of any testing procedure. In our studies at the

doses described in intact awake dogs, intravenously administered dipyridamole caused no reduction in systemic arterial pressure in contrast to the reported decrease in arterial pressure after intravenous administration of dipyridamole in anesthetized open chest animals.[41,47,54–56] In anesthetized animals we have also found that arterial pressure decreased after intravenous administration of dipyridamole.

Myocardial uptake of imaging agent proportional to coronary flow: The second basic physiologic requirement of any method for assessing coronary flow reserve is that the myocardial uptake of the imaging agent be proportional to flow at high coronary flow rates of at least 4 times resting levels. An agent whose uptake is not related to flow will be insensitive for detecting mild stenoses and an agent whose myocardial uptake is linearly related to flow will be the most sensitive. The myocardial uptake of thallium-201 is linearly proportional to flow at resting control levels down to zero,[1,9,10,24,57] but at higher flow levels necessary to assess coronary flow reserve thallium uptake is not proportional to flow. Strauss et al.[57] reported that the percent change in myocardial uptake of thallium-201 by tissue counting was 40 to 50 percent of the increase in coronary flow over resting control values measured with microspheres. We also found that the maximal thallium uptake by tissue counting during peak coronary vasodilatation after dipyridamole was only 50 to 60 percent higher than control levels. Weich et al.[58] reported that myocardial uptake of thallium-201 is proportional to flow (or extraction is constant) if the increase in coronary flow is induced by elevating myocardial oxygen demands as opposed to pharmacologic coronary vasodilatation, which does not increase myocardial oxygen requirements. In that study thallium-201 extraction was measured at coronary flow levels 4 times normal induced with coronary vasodilators. However, that value of extraction was then compared with the myocardial extraction of thallium-201 during electrical pacing, which is known to increase coronary flow by only 150 percent or less, even at rates up to 300 beats/min.[59–61] Thus, the extraction during pacing was not measured at flow rates comparable with those during coronary vasodilatation. The conclusions of that study are therefore open to question. More recently Weich et al.[62] reported that extraction of thallium-201 by the myocardium decreased logarithmically with increasing coronary flow produced with vasodilators. The predominant current evidence suggests that thallium uptake in the myocardium is increased as coronary flow increases regardless of the stimulus but is not linearly related to flow at flow rates higher than resting control values. At these high flow rates thallium-201 uptake increases by approximately one half of the increase in coronary flow statistically. However, there is sufficient variability in this proportion to prevent using uptake of thallium-201 as a quantitative index of flow changes.

Mechanisms affecting thallium imaging defects: Perfusion defects in thallium-201 myocardial images are produced predominantly by regional abnormalities of flow distribution. However, to the extent that thallium behaves like potassium, an additional mechanism may play a role. In areas of myocardial ischemia or injury, the uptake of potassium and the uptake of thallium are proportionately reduced on a metabolic basis.[62] For example, perfusion of a coronary artery at normal flow rates with unoxygenated blood produces regional myocardial ischemia with a normal volume of coronary flow. Thallium images demonstrate defects in the distribution of the coronary artery perfused with deoxygenated blood.[63] The relative importance of this metabolic mechanism in producing image defects over and above defects produced by regional flow abnormalities depends on the severity of the stenosis and myocardial oxygen requirements. Despite the problems outlined in the introduction we utilized external myocardial imaging in this study rather than tissue counting for several reasons. First, we wished to evaluate the imaging technique as it is used clinically, including the recognized problems of external imaging. Second, the experimental model was developed for repetitive studies using various types and doses of coronary vasodilators, different imaging agents and stenoses of differing severity, all using each dog as his own control. This approach is not possible with an experimental design in which myocardial tissue counting requires sacrifice of the animal.

Implication: Although myocardial uptake of thallium-201 is not linearly related to blood flow at high flow rates, this agent is the best currently available for myocardial perfusion studies in man. Experimental data suggest that myocardial imaging during pharmacologic coronary vasodilatation is an excellent method for noninvasively assessing regional coronary flow reserve and the physiologic significance of moderate coronary stenoses. Whether this approach will be more sensitive or specific than exercise testing in man will require clinical evaluation.

Acknowledgment

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Noninvasive Assessment of Coronary Stenoses by Myocardial Imaging During Pharmacologic Coronary Vasodilatation

II. Clinical Methodology and Feasibility

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A noninvasive method has been developed utilizing myocardial imaging of thallium-201 injected intravenously at rest and during coronary vasodilatation induced with intravenously administered dipyridamole, a potent selective coronary vasodilator. The method has been validated in experimental animals and shown to be more sensitive than exercise imaging in identifying moderate experimental coronary stenoses. This report describes the clinical feasibility and methodology of applying the technique to man. Study of a total of 162 myocardial perfusion images in 62 patients revealed the following: (1) The quality of myocardial perfusion images of thallium-201 injected during coronary vasodilatation induced with intravenously administered dipyridamole was equal to or better than that of myocardial images of thallium-201 injected during treadmill stress. (2) Myocardial uptake of thallium-201 measured with external imaging was considerably greater during dipyridamole-induced coronary vasodilatation than during treadmill stress. (3) The optimal dose rate of intravenously administered dipyridamole for this imaging technique was 0.142 mg/kg per min for 4 minutes with the thallium injected in the 3rd to 4th minute after completion of infusion while the patient was upright, walking in place. (4) With this dose rate regimen, side effects were minimal except for the occasional development of angina pectoris; the latter was eliminated by intravenous administration of aminophylline, a complete and virtually instantaneous antagonist of dipyridamole, after thallium had been taken up by the myocardium. This new method is therefore applicable to man and the initial results warrant a larger clinical study in order to define the diagnostic sensitivity and specificity of the technique.

Assessment of the hemodynamic significance of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation has previously been described in animals and man.[1–3] However, these initial studies were carried out during coronary arteriography and, as invasive procedures, were of limited clinical applicability although they served to establish the validity of measuring coronary flow reserve for evaluating coronary disease. More recently the basic physiologic requirements of a noninvasive method have been described in experimental animals[4,5] and validated by comparison with independent measurements of the pressure-flow characteristics of stenoses being studied.[5] The new technique utilizes myocardial imaging of thallium-201 during coronary vasodilatation induced with intravenously administered dipyridamole (Persantine®). Although there has been extensive experience with the intravenous administration of this agent in Europe, its clinical use outside the United States has not been for diagnostic myocardial imaging purposes. Therefore, questions remained regarding optimal intravenous dose rate regimens, timing of the injection of thal-

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lium-201 in relation to dipyridamole infusion and the effect of body position (supine, sitting or standing) on the quality of thallium perfusion images and potential side effects. Accordingly, this study of a small series of patients was undertaken to determine whether the technical procedures developed in animals were feasible and optimal for producing high quality images in man. The study was not intended to determine the diagnostic sensitivity and specificity of the dipyridamole-thallium technique, which will be described separately for a large series of patients. The current report addresses solely the problems of feasibility and methodology in man.

Methods

Patients: A total of 62 patients undergoing diagnostic coronary arteriography and exercise stress testing for suspected coronary artery disease were studied with one of several different experimental protocols. After discussion with each patient, a written consent form describing the procedure and its potential risks and benefits was signed by the patient. Patients were hospitalized for initial clinical evaluation of suspected coronary disease. History, physical examination, routine laboratory tests, chest X-ray film and resting electrocardiogram were obtained. A standard treadmill stress test using the Bruce protocol[6,7] was then performed to determine each patient's maximal duration on the treadmill. The next day diagnostic coronary arteriography was performed using the Judkins femoral approach; 35 mm cineangiograms of the coronary arteries were obtained in multiple views using a General Electric Floricon 300 X-ray system with a resolving power of 100 lines/inch (39.4/cm).

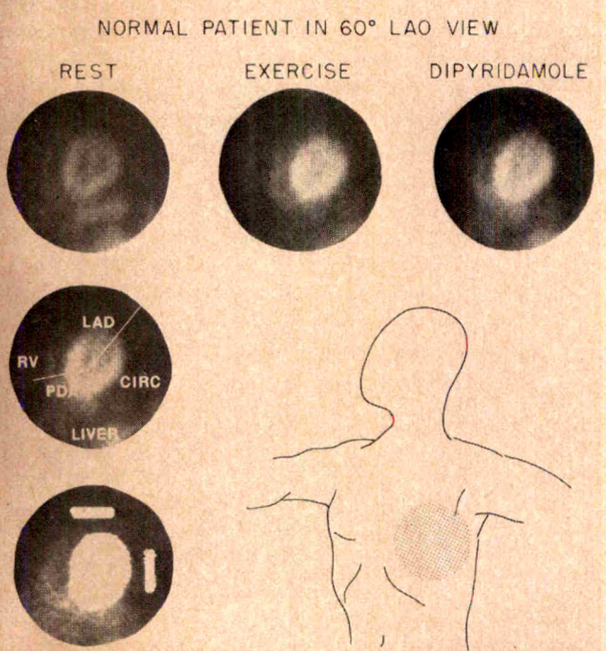

FIGURE 1. Myocardial images of a patient with normal coronary arteries in whom thallium-201 was injected at rest **(upper left),** during maximal treadmill exercise **(upper middle)** and after intravenous infusion of dipyridamole **(upper right).** All images are computer reproductions processed identically with 5 percent background subtraction for illustrative purposes. The quality of the dipyridamole image is comparable with that of the exercise image. Myocardial to background activity ratios were 2.2 at rest, 2.6 during exercise and 3.3 after dipyridamole. Orientation of images relative to human anatomy is shown with the distribution of the left anterior descending (LAD), left circumflex (CIRC) and posterior descending (PDA) coronary arteries. The **lowest panel** illustrates regions of interest for determining myocardial and background activities. RV = right ventricle.

Exercise thallium perfusion imaging: The day after coronary arteriography patients were taken to the Nuclear Medicine laboratory and 1.5 to 2.0 millicuries (mCi) of thallium-201 (New England Nuclear, Boston, Massachusetts) was injected intravenously with the patient standing. Twenty to 30 minutes later 300,000 count myocardial images were obtained with an Ohio Nuclear series 100 gamma camera in 30°, 45°, 60° left anterior oblique, left lateral and anterior posterior views. Images were recorded on Polaroid® film and also collected by a Nova II miniprocessor adapted for nuclear medicine applications (Medical Data System Corporation, Ann Arbor, Michigan) with a 128 × 128 display, dual disc drive, magnetic tape storage and software for localizing areas of interest by light pen for analysis of activity. Patients were then discharged and 1 week or more later, after residual thallium activity was no longer detectable in the heart, an exercise thallium perfusion image was obtained as follows: A second treadmill stress test was performed using the Bruce protocol. Thallium-201, 1.5 to 2.0 mCi was then injected intravenously 1 minute before the maximal duration of exercise observed in the first treadmill test. Exercise was continued for 1 minute. As soon as possible after recovery from exercise, patients underwent myocardial imaging, usually in less than 5 minutes after the treadmill was stopped; 300,000 count images of the heart were obtained in standard views as described. Fifty-seven of the 62 patients had resting and exercise images under this protocol to determine the effect of exercise on thallium uptake.

Dipyridamole thallium perfusion imaging: Thirty-eight of these 57 patients returned to the Nuclear Medicine laboratory 1 week or more after the exercise thallium image for a dipyridamole thallium test. A 19 gauge butterfly needle was placed in a large forearm or antecubital vein and taped securely in place. Injection of dipyridamole into small veins on the dorsum of the hand often resulted in a localized burning discomfort that did not occur with injection into large forearm veins. Precordial electrocardiographic leads were attached in the manner used for exercise testing. Baseline electrocardiogram and blood pressure were obtained. With the patient supine, intravenous infusion of dipyridamole (Boehringer Ingelheim, Elmsford, New York) was begun at an infusion rate of 0.142 mg/kg per min for 4 minutes using a Harvard model 551 infusion pump in which the standard single turn potentiometer for speed control had been replaced by a 10 turn potentiometer for more exact regulation of the rate of infusion. The readings of the 10 turn potentiometer had been previously calibrated in terms of cubic centimeters per minute by graduated cylinder and stopwatch for 5 kg steps ranging from 65 to 105 kg body weight. The electrocardiogram and blood pressure were recorded at 1 minute intervals during the infusion and for 15 minutes afterward or until baseline levels returned. In 10 of these previously exercised patients thallium-201, 1.5 to 2.0 mCi, was injected at the 4th minute after completion of the dipyridamole infusion while the patient remained supine. Twenty-eight previously exercised patients were brought to the standing position at the 2nd or 3rd minute after the end of the dipyridamole infusion and walked in place. Thallium was then injected at the 5th minute after completion of dipyridamole infusion while the patient continued walking in place for 3 to 5 minutes after injection of thallium. The patient then resumed the supine position. Twenty to 30 minutes after injection of thallium, standard myocardial images were again obtained as described. The time interval be-

tween thallium injection and imaging was later reduced to 5 minutes or less. In six patients three different dose rate regimens of dipyridamole were used to establish the optimal regimen for imaging purposes.

Analysis of thallium images: Original Polaroid photographs of myocardial perfusion images were interpreted independently by three observers and subsequently read again by a group of three observers together for a "consensus" interpretation. Images were analyzed quantitatively as follows: The resting control myocardial image was displayed on a persistence oscilloscope and the heart outlined with a light pen. Two separate representative background areas were also outlined. The contour of these areas of interest was stored in computer memory and then applied to all other images of a given patient so that areas of interest would be identical for that patient. Because the heart was not always located in the same position in different images of a patient, a computer program was developed to translate an image until the area of interest outline determined in the resting image was visually superimposed on the exercise or dipyridamole image. The activity in each area of interest was normalized for duration of imaging, dose of thallium injected in millicuries and number of channels in the area of interest. Units of activity were thus expressed as counts per minute per channel per millicurie injected. The quality of the images and the relative myocardial uptake of thallium were quantitatively evaluated in terms of myocardial to background activity ratios using the average of the two background areas. The results of analyzing exercise and dipyridamole images were expressed as percent of resting control values. For illustrations shown all images were processed identically with 5 percent background subtraction.

Analysis of data: The effects of maximal treadmill exercise and dipyridamole on thallium activity in myocardial areas, background areas and myocardial to background activity ratios of 162 thallium myocardial images from 62 patients were analyzed in five overlapping groups as follows: (1) 57 patients with resting and exercise thallium perfusion images studied to compare exercise and resting myocardial images with paired t testing; (2) 40 patients with resting and standard dipyridamole thallium images in the supine or standing position studied to compare dipyridamole and resting myocardial images with paired t testing; (3) 38 patients with resting, exercise and dipyridamole perfusion images studied to compare exercise and dipyridamole images with paired t testing; (4) 6 patients with thallium images after standard infusion and three different nonstandard dipyridamole dose rate regimens to determine the optimal standard dipyridamole dose rate for imaging purposes; and (5) 43 patients receiving dipyridamole under a standard or nonstandard dose regimen to evaluate potential side effects.

Results

Normal patient: Figure 1 shows an example of a myocardial perfusion image of a normal patient with thallium-201 injected at rest, during treadmill exercise and after intravenous administration of dipyridamole. The exercise image was more distinct than the resting image with a greater myocardial to background ratio. The right ventricle was also visible as a crescent of activity at the left of the image. The quality of the dipyridamole image was equal to that of the exercise image with a comparable myocardial background ratio and equal visualization of the right ventricle.

Exercise and dipyridamole images during exercise versus rest: Although the exercise and dipyridamole images were comparable in quality and visual appearance, the changes in myocardial and background activity of the exercise image as compared with the resting image were different from those for dipyridamole. Figure 2 shows the average counting activity of myocardial areas, background areas and myocardial to background ratios of each exercise image expressed as a percent of values from the resting control image of each patient. During exercise the counts per minute per channel per unit dose of thallium injected for the myocardial area decreased to 92.3 ± 15.8 (mean ± 1 standard deviation) percent of the resting control image and this decrease was statistically

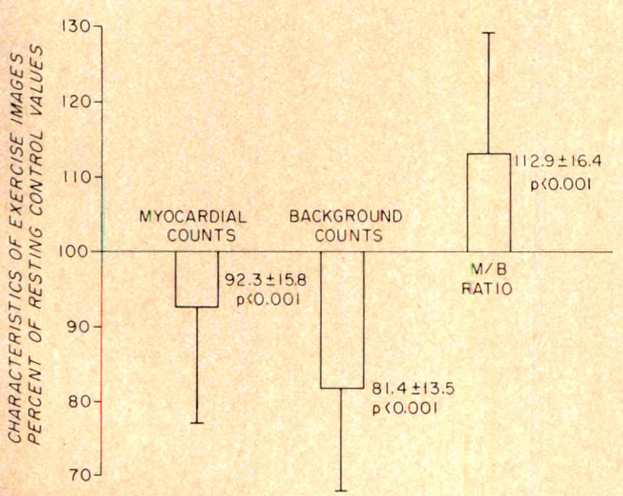

FIGURE 2. Changes in myocardial and background activity of exercise thallium images in 57 patients expressed as percent of resting control values. Activity of the myocardial area decreased significantly below control resting values. Background activity decreased to a greater and statistically significant extent. Myocardial to background (M/B) ratios increased significantly primarily because of the decrease in background activity. Significance is shown according to a paired t test comparing exercise and resting values for each patient. Bars indicate ±1 standard deviation. p = probability.

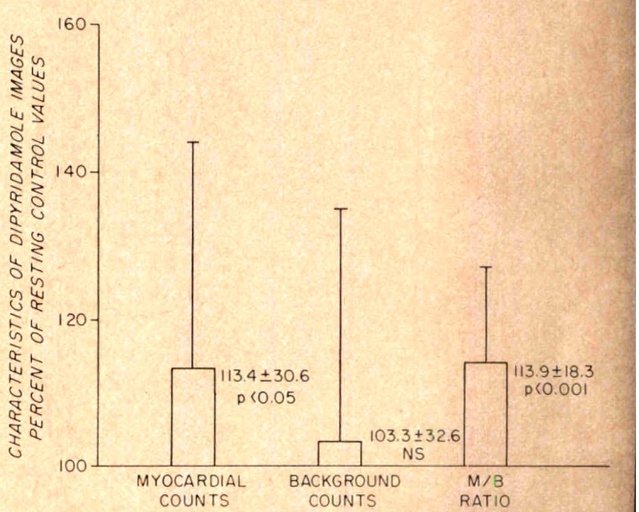

FIGURE 3. Changes in myocardial and background activity of dipyridamole thallium images in 40 patients expressed as a percent of resting control values. Activity of the myocardial area increased significantly. Background activity increased somewhat but the change was not statistically significant. Myocardial to background (M/B) ratios increased significantly primarily because of the increase in myocardial activity. Significance is shown according to paired t test comparing dipyridamole and resting values for each patient. Bars indicate ±1 standard deviation. NS = difference not significant.

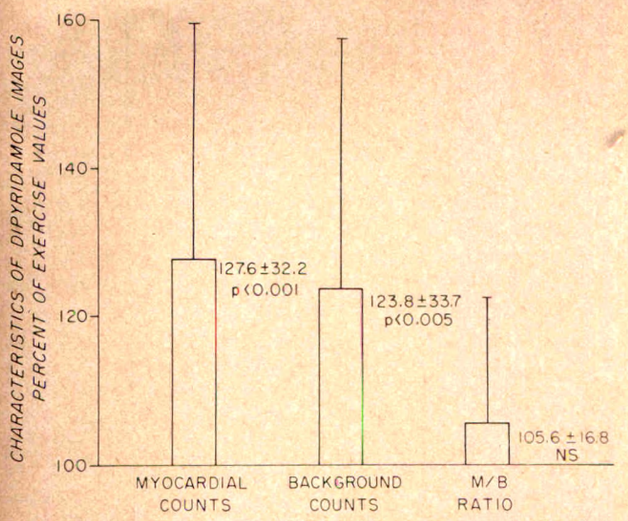

FIGURE 4. Comparison of myocardial (M) and background (B) activity of dipyridamole and exercise thallium images in 38 patients. Activity of the dipyridamole images are expressed as a percent of exercise values. Both myocardial and background activity of the dipyridamole images were significantly greater than for exercise images. Significance is shown according to paired *t* test comparing dipyridamole and exercise values for each patient. Bars indicate ±1 standard deviation.

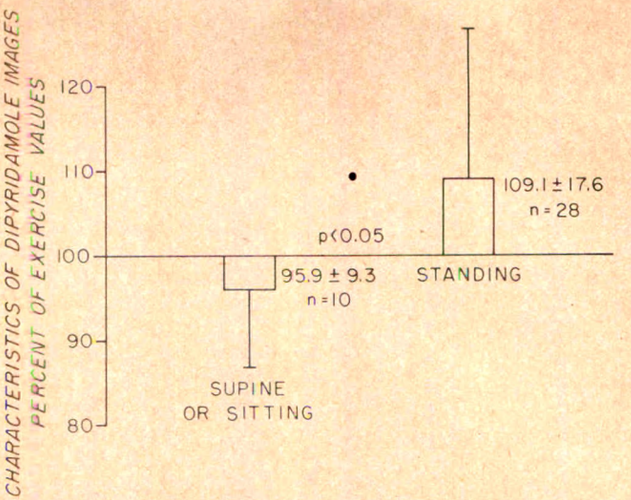

FIGURE 5. Effect of body position at the time of thallium injection on the myocardial to background activity ratios of myocardial images taken after intravenous administration of dipyridamole in 38 patients and expressed as percent of exercise values. The quality of images as reflected in myocardial to background ratios was significantly improved by injecting the thallium with the patient in the standing position. The *P* value is shown according to an unpaired *t* test comparing standing with supine or sitting patients. Bars indicate ±1 standard deviation. n = number of patients.

significant ($P < 0.001$). The counts in the background area decreased to a greater extent, to 81.4 ± 13.5 percent of resting counts, also a statistically significant difference ($P < 0.001$). The myocardial to background ratio therefore increased significantly during exercise to 112.9 ± 16.4 percent of control myocardial to background ratios thereby resulting in an improvement in the visual appearance of the image ($P < 0.001$).

Figure 3 shows data for dipyridamole images presented in comparable fashion. The counts per minute per channel per dose of thallium in myocardial areas of dipyridamole images increased to 113.4 ± 30.6 percent of activity in resting control images ($P < 0.05$). Counts in background areas also increased but to a lesser and statistically insignificant extent than in myocardial areas. The average myocardial to background ratio therefore increased to 113.9 ± 18.3 percent of resting ratios ($P < 0.001$) with a corresponding improvement in image quality as compared with the resting image.

Direct comparison of exercise and dipyridamole images (Fig. 4): Activity of myocardial areas, background areas and myocardial to background ratio of each dipyridamole image was expressed as a percent of values from the exercise image of the same patient. Counts per minute per channel per dose of thallium in the myocardial areas on the dipyridamole images were higher than on the exercise images, averaging 127.6 ± 32.2 percent of the exercise image ($P < 0.001$). Counts of the background areas of dipyridamole images were also significantly higher than on exercise images. Myocardial to background ratios of dipyridamole images were slightly higher than for exercise images, but the difference was not statistically significant. These results indicate that both exercise and dipyridamole improved the quality and myocardial to background ratios of thallium perfusion images but by different mechanisms. During exercise the improved myocardial to background ratio resulted primarily from a reduction in background activity whereas after infusion of dipyridamole the improved myocardial to background ratio resulted primarily from an increase in myocardial activity.

Effect of body position at the time of thallium injection on myocardial perfusion images after infusion of dipyridamole (Fig. 5): In patients who remained supine during dipyridamole infusion and injection of thallium, the resulting images had myocardial to background ratios that were only 95.9 ± 9.3 percent of exercise ratios. However, in patients who rose to the standing position with walking in place for 1 to 2 minutes before and 3 to 5 minutes after injection of thallium, myocardial perfusion images demonstrated higher myocardial to background ratios of 109.1 ± 17.6 percent of exercise ratios for the same patients. The difference between standing and supine or sitting myocardial to background ratios for dipyridamole images expressed as a percent of exercise ratios was statistically significant. If only standing patients are considered the myocardial to background ratio for dipyridamole images of 2.3 ± 0.5 is slightly but significantly higher than the ratio for exercise images of 2.1 ± 0.4 by paired *t* testing ($P < 0.02$).

Effects of various dose rate regimens of dipyridamole on myocardial to background ratios of images and blood pressure: Either smaller doses or slower dose rate infusions of dipyridamole failed to increase myocardial to background ratios to the same extent as the standard regimen of 0.142 mg/kg per min for 4 minutes (0.57 mg/kg total dose). In four patients this same total dose of 0.57 mg/kg was given as an intravenous bolus injection. The fourth patient had significant orthostatic hypotension with blood pressure decreasing from 120/75 to 80/40 mm Hg when standing although while supine his pressure had remained normal. After he resumed the supine position with elevation of his legs, his blood pressure immediately returned to 122/70 mm Hg without sequelae. He had no angina pectoris or electrocardiographic changes, showed no subsequent enzyme changes and had normal coronary arteriograms. No further trials of this bolus regimen were undertaken. The effects of the procedure, that is, combined dipyridamole and standing-in-place-walking, on blood pressure and heart rate were as follows: Control supine systolic

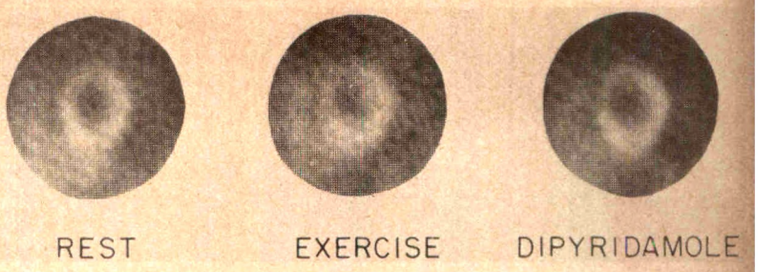

FIGURE 6. Myocardial images in 30° left anterior oblique view of a patient with isolated disease of the left anterior descending coronary artery after intravenous administration of thallium-201 at rest **(left),** during maximal treadmill exercise **(center)** and after intravenous administration of dipyridamole **(right).** At rest no perfusion defect was apparent. In the exercise image a probable defect appeared in the left anterior descending coronary arterial distribution. In the dipyridamole image this defect was quite distinct as a thinning in the activity of the left ventricular wall. The quality and sharpness of the dipyridamole image are equal to or better than those of the exercise image. All images were processed identically with 5 percent background subtraction.

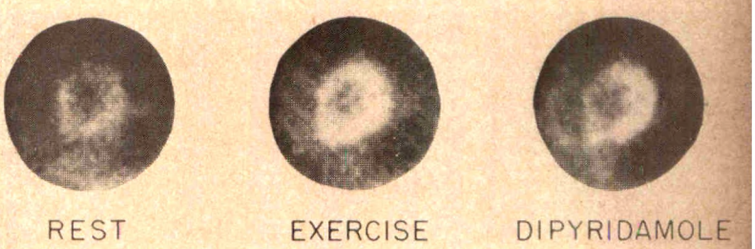

FIGURE 7. Myocardial images in 45° left anterior oblique view of a patient with isolated disease of the left anterior descending coronary artery after intravenous injection of thallium-201 at rest **(left),** during maximal treadmill exercise **(center)** and after intravenous infusion of dipyridamole **(right).** At rest no defect was apparent. The exercise image in the same view also failed to show a definite abnormality. However, the dipyridamole image showed a large distinct definite abnormality. All images were processed identically with 5 percent background subtraction.

blood pressure by cuff was 130 ± 17 mm Hg and decreased to 121 ± 18 mm Hg during standing-in-place-walking after dipyridamole (P <0.001). Corresponding changes for diastolic blood pressure were 81 ± 10 mm Hg down to 74 ± 10 mm Hg (P <0.001). Control supine heart rate was 64 ± 8 beats/min and increased to 88 ± 12 beats/min during standing after dipyridamole (P <0.001).

Patients with isolated left anterior coronary artery disease: Figure 6 illustrates thallium perfusion images of a patient at rest, during treadmill exercise and after dipyridamole infusion. At rest the image was normal with equal activity in the left anterior descending, left circumflex and right coronary arterial distributions. During exercise there was less activity in the left anterior descending distribution arterial corresponding to the location of coronary disease and this relative perfusion deficit was as distinct or more distinct in the dipyridamole image than in the exercise image. Figure 7 shows another patient who had a normal resting image as well as a probably normal exercise image in this view. However, the dipyridamole image showed a definite and severe perfusion defect in the distribution of left anterior descending coronary artery disease. This patient also had moderately severe angina pectoris 5 minutes after completion of dipyridamole infusion and 1 minute after thallium injection. The angina pectoris was also associated with S-T segment depression. Both chest pain and electrocardiographic changes disappeared within several seconds after the intravenous administration of 125 mg of aminophylline, which terminated the coronary vasodilatory effects of dipyridamole after the thallium had been taken up by the myocardium.

Side effects: Of the 43 patients given dipyridamole, the patient who received a larger than standard dose rate was the only one who had a significant unexpected side effect, that is, orthostatic hypotension treated by resumption of the supine position and leg raising. Eighteen of the 43 patients (42 percent) had mild transient headache, 23 (53 percent) experienced mild transient facial flushing, 6 (14 percent) had mild transient nausea and 12 (28 percent) had mild fleeting angina pectoris that required no therapy. Two patients (5 percent) experienced significant angina pectoris that stopped immediately with intravenously administered aminophylline after thallium had been taken up by myocardium. High quality images showing perfusion abnormalities were obtained in both patients. The onset of angina pectoris after infusion of dipyridamole was gradual, developing over 3 to 4 minutes in each case. Therefore, there was sufficient time before giving aminophylline for complete thallium uptake by the myocardium with resulting good images of perfusion abnormalities. All but one patient stated that the dipyridamole test was preferable to the treadmill exercise test. The infusion imaging procedure was more easily performed and required less technician-physician time than exercise imaging.

Heart rate and myocardial to background ratios of dipyridamole images: Patients with the largest increases in heart rate after dipyridamole also showed the greatest increases in myocardial to background ratios of dipyridamole images, as shown in Table I. For this table, patients were ranked in sequential order from greatest to least increase in supine heart rate after dipyridamole infusion. Corresponding myocardial to background ratios of dipyridamole images were then listed beside heart rate change for each patient and the data were grouped into quartiles for statistical comparison. In addition, corresponding changes in heart rate, blood pressure-heart rate product and myocardial to background ratios during exercise with degree of exercise impairment were listed for each ranked patient and averaged for each quartile for comparative purposes.

The results suggest that there is a variable dose effect of a fixed rate, milligram per kilogram per minute infusion of dipyridamole on heart rate and myocardial to background ratios of dipyridamole images. Patients with larger increases in heart rate during exercise did not have higher myocardial to background ratios in exercise images. The maximal pressure-rate product and severity of exercise impairment were not significantly different among these quartiles. Therefore, differences in heart rate response cannot be ascribed to severity of coronary disease but must be associated wih a variable response to a fixed, per kilogram dose of dipyridamole. It may therefore be possible to titrate the dose rate of dipyridamole infusion for each patient up to a fixed limit using supine heart rate response as an end point of the dose effect in order to achieve a more uniform maximal vasodilatory effect. The efficacy of

TABLE I

Relation of Increase in Heart Rate and Myocardial/Background Ratios After Dipyridamole and Exercise

Quartile	Dipyridamole % ΔHR	Dipyridamole M/B Dipyr / M/B Rest	Dipyridamole PRP	Exercise % ΔHR	Exercise M/B Exer / M/B Rest	Exercise % FAI
1	46 ± 9	1.3 ± 0.2	222 ± 65	100 ± 43	1.1 ± 0.1	40 ± 27
2	31 ± 4*	1.2 ± 0.1	234 ± 77	102 ± 42	1.1 ± 0.1	29 ± 18
		P <0.046	NS	NS	NS	NS
3	23 ± 3*	1.1 ± 0.2	195 ± 61	75 ± 15	1.1 ± 0.2	29 ± 19
		P <0.034	NS	NS	NS	NS
4	12 ± 4*	1.0 ± 0.1*	186 ± 52	64 ± 26	1.0 ± 0.2	44 ± 16
			NS	*P* <0.04	NS	NS

*Significant difference of each quartile compared with the 1st quartile with a probability (*P*) value of $P = 0.001$ or less.

Dipyr = dipyridamole; Exer = exercise; FAI = functional aerobic impairment expressed as percent impairment of values in normal age-sex matched control subjects; M/B = myocardial/background; NS = nonsignificant difference from value in first quartile; % Δ = average percent increase ±1 standard deviation; PRP = maximal exercise pressure-rate product ÷ 100.

dose tritration as compared to a fixed dose rate infusion on diagnostic sensitivity and specificity is currently being examined.

Discussion

Cardiovascular effects and optimal dose rate regimen of dipyridamole: The most important questions about the dipyridamole-thallium method for assessing the physiologic significance of coronary disease involve the effectiveness of dipyridamole as a selective coronary vasodilator and the dose-rate regimen providing optimal image quality with least side effects. Table II shows the reported range of dose-rates.[8–18] Figure 8 shows the cardiovascular effects of intravenous administration of dipyridamole in 28 patients reported on by Tauchert et al.[8,9] The changes expressed as percent of control resting values were calculated for this figure from the original data listed in tables for individual patients by Tauchert (data extracted from Tables 3 and 4 of reference 8). The wide standard deviation is due to a less than 3 times response in three patients. Coronary flow increased to an average of four times baseline control values with a minor but statistically significant increase in cardiac output and heart rate and decrease in aortic pressure. The dose-rate of dipyridamole producing these effects was 5 mg intravenously every 2 minutes for a total of 0.5 mg/kg. Hilger[10] measured the change in coronary sinus oxygen saturation of 10 resting patients during intravenous administration of 50 mg of dipyridamole over 15 minutes. Coronary sinus oxygen saturation increased by more than 200 percent (to 3 times resting values) reflecting corresponding changes in coronary flow. Smaller doses given more rapidly failed to produce comparable responses. Hilger[10] utilized a larger total dose than our standard regimen of 0.56 mg/kg (39.2 mg for a 70 kg man) but gave it at a slower rate over 10 to 15 minutes as opposed to our 4 minute infusion. Several investigators have used larger doses and reported significant side effects. Wilcken et al.[11] gave 0.6 mg/kg of dipyridamole intravenously over 5 minutes to 10 normal subjects and 3 patients with coronary disease. The three patients manifested severe angina pectoris with marked S-T depression for several hours with normal blood pressure and without subsequent enzyme changes or permanent sequelae. Mantero and Conti[12] also reported significant

TABLE II

Reported Dose Rates of Intravenous Dipyridamole Administered to Patients

Reference	Dose	Duration of Infusion	Patients (no.)
13	20 mg	2 min	18
14	10 mg	Bolus dose	9
8	0.5 mg/kg	2.5 mg/min	28
15	0.5 mg/kg	2.5 mg/min	32
10	50 mg	15 min	10
16	0.5 mg/kg	10 min	60
11	0.6 mg/kg	5 min	13
12	80–100 mg	40–60 mg/20 min	109
17	20 mg	Bolus dose	9
18	0.43–0.86 mg/kg	Bolus dose	7

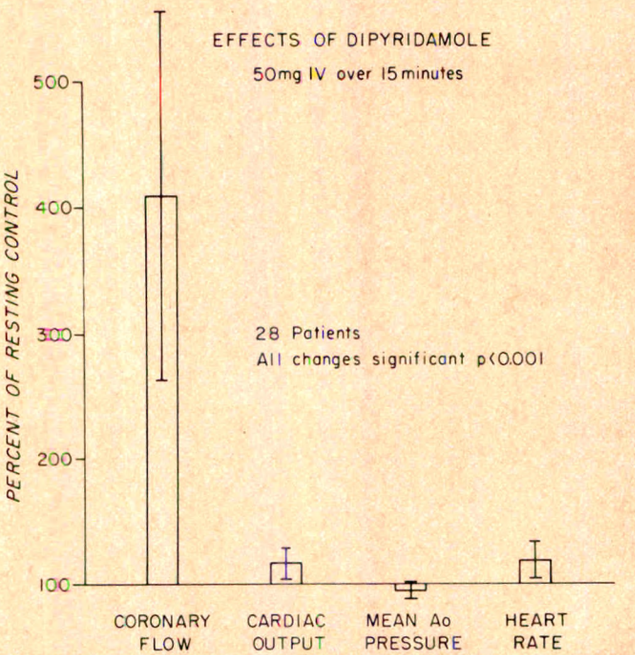

FIGURE 8. Effect of intravenously administered dipyridamole on heart rate, central aortic (Ao) mean pressure, cardiac output and coronary flow measured with the argon technique. Changes caused by dipyridamole are expressed as percent of control resting values. Results shown in this figure were calculated from data listed for individual patients as reported by Tauchert et al.[8] (data extracted from their Tables 3 and 4). The dose-rate of intravenous (IV) infusion of dipyridamole used by Tauchert et al. was 5 mg every 2 minutes for a total dose of 0.5 mg/kg. Coronary flow increased to approximately 4 times resting values with relatively minor changes in cardiac output, aortic pressure and heart rate. Bars indicate ±1 standard deviation.

chest pain in 22 of 109 patients with coronary disease in whom very large doses of 80 to 100 mg of dipyridamole were infused over a 20 minute period. However, in neither of these studies was aminophylline used to terminate the effects of dipyridamole.

Mechanisms leading to angina pectoris or myocardial ischemia: After intravenous administration of dipyridamole myocardial oxygen consumption reportedly decreases or increases slightly in anesthetized dogs[19,20] and increases 20[14,15] to 100 percent[8] in man. There are therefore two potential causes for ischemia after infusion of this drug. One is the modest increase in myocardial oxygen consumption. However, most patients in our study who demonstrated perfusion defects due to coronary disease had no angina or S-T changes. The second and most likely mechanism arises from the pressure-flow relations characterizing coronary stenoses previously described[21–24] (and Gould LK, unpublished data). As flow velocity increases through a coronary stenosis the energy or pressure losses due to viscous friction increase in linear proportion to flow velocity, and pressure losses due to flow separation (vortex shedding) increase as a function of the square of velocity. Thus, at increased coronary flow the pressure loss is greater than at resting coronary flow and distal coronary perfusion pressure is correspondingly less despite increased flow in the epicardial artery. With coronary vasodilatation, coronary flow and pressure gradient increase across the stenosis, distal coronary perfusion pressure decreases and the subendocardium may become underperfused.

Such a mechanism may explain the experimental results of previous workers[25–27] who found impaired subendocardial perfusion during coronary vasodilatation or exercise in animals with proximal coronary stenoses. Although demonstrated experimentally, decreased perfusion of the subendocardium during coronary vasodilatation in the presence of coronary stenoses cannot be definitively proved in man by the microsphere technique used in animals, which requires counting tissue samples. However, Figures 6 and 7 do demonstrate particularly suggestive abnormalities in the myocardial perfusion images during dipyridamole-induced coronary vasodilatation. These images show thinning of the myocardial activity of the left ventricular wall that, in combination with chest pain and S-T segment depression in the second patient, strongly suggests hypoperfusion of the subendocardium. Thus, we believe that angina pectoris and subendocardial ischemia, which may occur in the presence of coronary disease during dipyridamole infusion, are inherent in the fact of coronary vasodilatation and are probably not specific for the type of coronary vasodilator as such.

Nevertheless, because myocardial oxygen demands are not increased as much by dipyridamole as by exercise, an imaging method using a coronary vasodilator will permit greater coronary dilatation and greater differences in regional myocardial blood flow before ischemia develops as compared with exercise stress. These greater differences in regional coronary flow distribution obtainable by coronary vasodilators may therefore make a pharmacologic method more sensitive than exercise stress in identifying early coronary lesions. The sensitivity of the dipyridamole method or other pharmacologic techniques thus depends on the adequacy of coronary vasodilatation. The dose rate of dipyridamole infusion is therefore crucial to the effectiveness and safety of the dipyridamole method. Doses of less than 0.142 mg/kg per min for 4 minutes did not consistently produce high quality myocardial images. Titration of the dose according to heart rate response may provide a means of producing more uniform maximal drug effect. Angina pectoris may also occur but the use of intravenously administered aminophylline as a relatively instantaneous and complete antagonist of dipyridamole provides control of its effects and a large safety factor in the dipyridamole method.[10,16,28–31] Any other coronary vasodilator that was more potent than dipyridamole would further increase the sensitivity of imaging techniques for identifying coronary disease. However, the risk of subendocardial ischemia might also increase and therefore an antagonist would be required to terminate the effects of the coronary vasodilator if necessary.

Coronary or myocardial steal after dipyridamole: Intravenous administration of dipyridamole or other potent coronary vasodilators reportedly may cause "coronary or myocardial steal"[11,12,25,31–36]; although applied loosely, the term "steal" is defined as an absolute reduction in coronary flow to an area of myocardium, particularly the endocardium, during some stimulus for coronary vasodilatation. The safety of dipyridamole has therefore been questioned. The expression "coronary steal" is not specific and refers to a spectrum of pressure-flow changes that are more clearly explained in terms of the pressure gradient-flow relation described in the preceding article.[5] With coronary vasodilatation the coronary pressure distal to a stenosis decreases as total flow in the epicardial artery increases.[1,2,5,21–23,31]

Under these hemodynamic conditions there are two circumstances in which the term "steal" has been applied. In the first case, for single vessel disease the coronary pressure distal to a stenosis might decrease enough so that pressure is inadequate to perfuse the endocardium despite an increase in total flow in the epicardial artery. In this case the underperfusion of the endocardium could be only relative with normal or increased absolute flow but reduced endocardial to epicardial flow ratios[31,35,36] that should *not* be called "steal." However, if the vasodilatory stimulus were great and the fall in coronary pressure distal to the stenosis were profound, as with severe stenoses or with combined coronary vasodilators and pacing, the absolute endocardial flow in cc/min per g of endocardium would decrease despite an adequate or even increased epicardial artery flow[25–27,31,35,36]; then epicardial "steal" might be an appropriate term. However, the terminology in this circumstance is debatable.[26,31] In the second case, for two (or more) vessel disease with collateral channels between the distal beds, a greater decrease in distal coronary pressure in one bed might shunt blood away from the other better perfused bed through the collateral channels with a decrease in absolute endocardial

flow[31,34–36]; "steal" would then be an appropriate term.

For any of these hemodynamic changes the final common result would be an imbalance between blood supply and demand regardless of whether exercise, pharmacologic coronary vasodilatation or progressively severe stenosis caused the abnormal hemodynamic conditions. Thus, if "coronary steal" with ischemia does occur after dipyridamole, it is of no greater consequence than ischemia induced by exercise. In either instance the stimulus producing ischemia should be removed by stopping exercise or by giving aminophylline in order to terminate the effects of dipyridamole. For imaging purposes the major point is that coronary vasodilators provide greater differences in regional perfusion before ischemia develops as compared with exercise, in which myocardial oxygen demands are increased greatly. Thus, perfusion defects in dipyridamole images are seldom associated with significant angina pectoris whereas defects in exercise images are commonly associated with significant angina.

Effect of body position at the time of injecting thallium: Body position has an important effect on myocardial to background ratios of perfusion images after dipyridamole. The quality of images and myocardial to background ratios are considerably improved by having the patient walk in place for 1 to 2 minutes before, during, and 3 to 5 minutes after the injection of thallium. We do not have a satisfactory explanation for this observation but one possibility is that pulmonary blood volume, transit time and capillary surface area are greater in the supine position than in the upright position.[37] Consequently, lung uptake of thallium is probably greater and therefore background activity greater in the supine than in the upright position. The upright position[37] or exercise,[38] or both, decreases pulmonary blood volume and transit time and would be expected to result in reduced lung uptake of thallium and improved myocardial to background ratios.

Effect of exercise on myocardial uptake of thallium on external images and the problem of background activity: The lack of increased counting activity in myocardial areas of exercise images was somewhat unexpected. For this reason 57 patients were studied to verify these results. Either no change or a reduction in activity of the myocardial area, as well as a greater reduction in background activity, was usually observed. These observations are compatible with two explanations: (1) Pulmonary transit time is reduced during exercise and there is less time than during rest for thallium uptake by the lungs; (2) in man coronary blood flow reportedly increases with exercise to a lesser extent than to the 4 times baseline levels (300 percent) increase occurring after administration of coronary vasodilators. Average increases in coronary flow during exercise previously reported range from 33 to 44 percent,[39] 49 to 77 percent,[40] 7 to 58 percent,[41] 222 to 272 percent[42] and 103 to 213 percent.[43] An increase of 331 percent was reported in one study[44] in which coronary flow was measured only during exercise with no resting control values; the reported increase was based on an estimated, not measured, resting coronary flow value and is therefore open to question. These relatively modest changes in coronary flow during exercise compared with the ranges after coronary vasodilators may not be sufficient to produce regional differences in thallium uptake that are measurable with external imaging, particularly if one considers that thallium is not taken up in proportion to increases in flow at high coronary flow levels.[45,46]

In addition, the interpretation of counting activity in areas of myocardium in thallium images is complicated by the activity of lung overlying the heart. In experimental animals we have studied this problem by imaging the thorax before and after removing the heart and replacing it with an equal-sized balloon filled with saline solution.[47] The true background activity in the region immediately in front of and behind the heart was much less than activity of adjacent image areas on either side of the heart. We therefore believe that counting activity in the area of the myocardium measured with external imaging is of limited validity as an indicator of qualitative directional changes in myocardial thallium uptake and coronary flow. Certainly, the activity in areas of myocardium in thallium images cannot be used as a quantitative measure of coronary flow because thallium uptake is not proportional to flow at high coronary flow rates and because true background activity behind the heart cannot be reliably predicted from activity in areas adjacent to the heart, thereby precluding background correction.

One possible solution to the problem of overlying background activity is the use of tomography to obtain cross-sectional images of the myocardium. Tomographic images would potentially reduce the effect of background activity, improve visualization of the posterior myocardium by eliminating overlapping myocardial structures and provide an indication of epicardial to endocardial flow distribution. However, the technology for high resolution tomographic imaging of the heart is in developmental stages and these advantages are potential, not proved.

Implications: Myocardial perfusion imaging with thallium-201 during coronary vasodilatation with intravenously administered dipyridamole is feasible as a routine diagnostic procedure in patients. However, it is necessary to pay careful attention to dose rates of infusion, timing of thallium injection, body position and proper monitoring of the patient's blood pressure, electrocardiogram and clinical symptoms. We also believe that patients with angina pectoris at rest should not be studied with dipyridamole because diagnostic image defects would be expected without introduction of a stress.

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New Serial Contrast Technique for Assessment of Left to Right Shunting Patent Ductus Arteriosus in the Neonate

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A new serial echocardiographic contrast technique for detection of patent ductus arteriosus has been developed and validated by clinical course (33 infants), surgical observations (13 infants) and autopsy observations (4 infants). A left to right shunting patent ductus arteriosus was demonstrated in 30 of 33 prospectively studied premature infants (mean weight 1,371 g) using this new contrast method. The demonstration of left to right ductal shunting was accomplished by hand injection of a nonviscous material (saline solution, 5 percent dextrose in water or the patient's own blood) through an umbilical arterial catheter placed with its tip located above the diaphragm during recording of a suprasternal notch echocardiogram. In positive studies, both the transverse aortic arch and right pulmonary artery were opacified. If no left to right shunt existed, only the transverse aortic arch was opacified.

This serial study helped elucidate the natural history of patent ductus arteriosus. Twenty-four of the 30 patients with a positive study initially had a left to right shunting patent ductus arteriosus without an audible murmur. Three of these patients with silent patent ductus arteriosus later had congestive heart failure and two required operative ligation of the patent ductus. The high rate of detection of silent patent ductus arteriosus and its bedside confirmation when suspected are important in the serial management of critically ill newborns with this condition. The test is safe and sensitive and it is useful for early demonstration of silent patent ductus arteriosus, for clarifying the origin of murmurs and for confirming spontaneous, operative or pharmacologic closure of a patent ductus arteriosus.

Clinical management of the premature infant with the respiratory distress syndrome is subject to many complications, one of which is patent ductus arteriosus.[1–4] The latter is usually suspected when a murmur is audible, peripheral pulses are increased, the heart is enlarged and increased pulmonary vascularity is evident in the thoracic roentgenogram. Echocardiography has been used in several recently reported studies[5–8] to assess left atrial and left ventricular dimensions, which can reflect increased pulmonary blood flow associated with the patent ductus arteriosus or with the effects of associated congestive heart failure, or both. Standard echocardiographic evaluation of infants with this condition has been performed in the anteroposterior (precordial) plane. A recent extension of echocardiography has been the imaging and measurement of the transverse aortic arch, right pulmonary artery and left atrium (Y′ left atrial dimension) in a superoinferior plane from the suprasternal notch.[9] The combination of precordial and suprasternal techniques has allowed a bidimensional evaluation of left atrial size, often detecting enlargement or shape distortion of the left atrium that may have been missed in the precordial examination.

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Concern has been expressed recently regarding the large patent ductus arteriosus that is "silent" and undetected using standard clinical criteria for noninvasive bedside identification. Thibeault et al.[10] confirmed the presence of a patent ductus arteriosus by taking a single thoracic roentgenogram during hand injection of angiographic contrast material through an umbilical arterial catheter placed in the thoracic aorta. Their study showed that the patent ductus arteriosus was "silent" in 22 of 27 premature infants at a mean age of 39 hours. Murmurs were never heard in 10 of these patients, and cardiomegaly was often present before the appearance of a murmur. Although this type of aortography is confirmatory, the technique involves injection of radiographic contrast material, use of ionizing radiation and performance of the single X-ray film at exactly the correct time. Gramiak et al.[11] and later Valdes-Cruz et al.[12,13] demonstrated that rapid hand injection of a sterile nonviscous material such as Cardiogreen® dye, saline solution, dextrose in water or the patient's own blood into a vessel or cardiac chamber produces a contrast echocardiogram that shows the internal limits of that structure and demonstrates the cardiac flow patterns in conditions such as intracardiac shunts or valve insufficiency.

In this investigation we developed and validated an arterial contrast echocardiographic technique that confirms the presence of a left to right shunting patent ductus arteriosus and elucidates more clearly its natural history in premature infants.

Methods

The only criterion for selection of infants for this study was the need to have a clinically indicated umbilical arterial catheter placed by the attending neonatologist. After explanation of the procedure and the risks involved, informed consent was obtained from the infant's parents under a Human Subjects approved protocol.

Technique: The tip of the umbilical arterial catheter was placed in the descending thoracic aorta between the third and sixth thoracic vertebrae. Its position was then checked with a thoracic roentgenogram. After a standard echocardiographic study, a suprasternal echocardiogram was obtained for imaging of the transverse aortic arch, right pulmonary artery and left atrium (Fig. 1). The echocardiogram was obtained

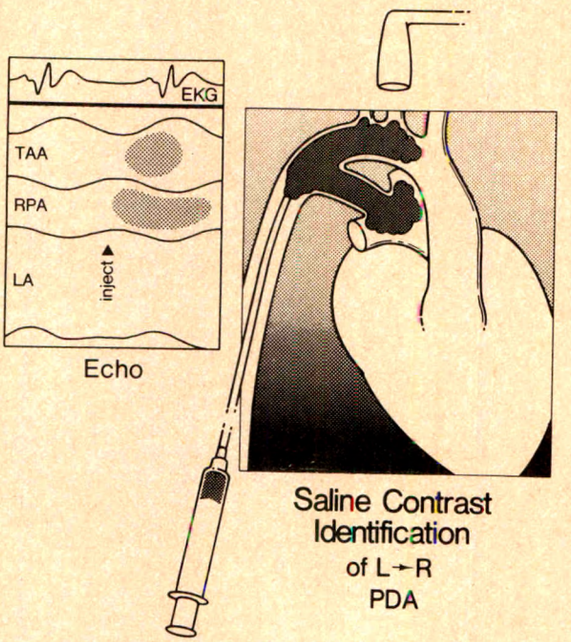


FIGURE 1 (above). Diagram **(right)** showing contrast material hand-injected through a catheter placed in the thoracic aorta during recording of a suprasternal notch echocardiogram. The transverse aortic arch fills. If a patent ductus arteriosus (PDA) is shunting left to right (L → R), the right pulmonary artery also fills. The echocardiogram (diagrammed at **left**) shows opacification in the otherwise clear transverse aortic arch (TAA) and right pulmonary artery (RPA) after injection. EKG = electrocardiogram; LA = left atrium.

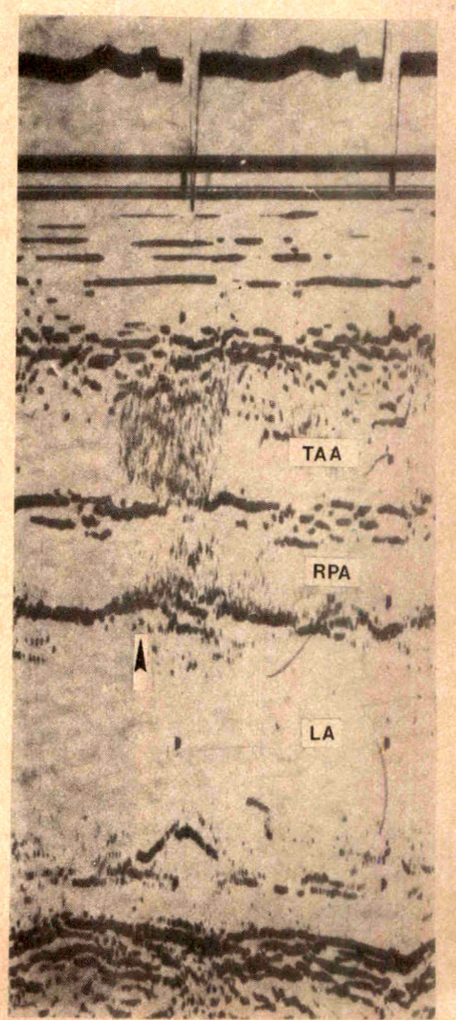


FIGURE 2 (right). Echoaortogram from a patient with a left to right shunting patent ductus arteriosus. The **arrow** shows the timing of injection. Contrast material opacifies the transverse aortic arch (TAA) and then the right pulmonary artery (RPA). Calibration markers are noted in the left atrium (LA).

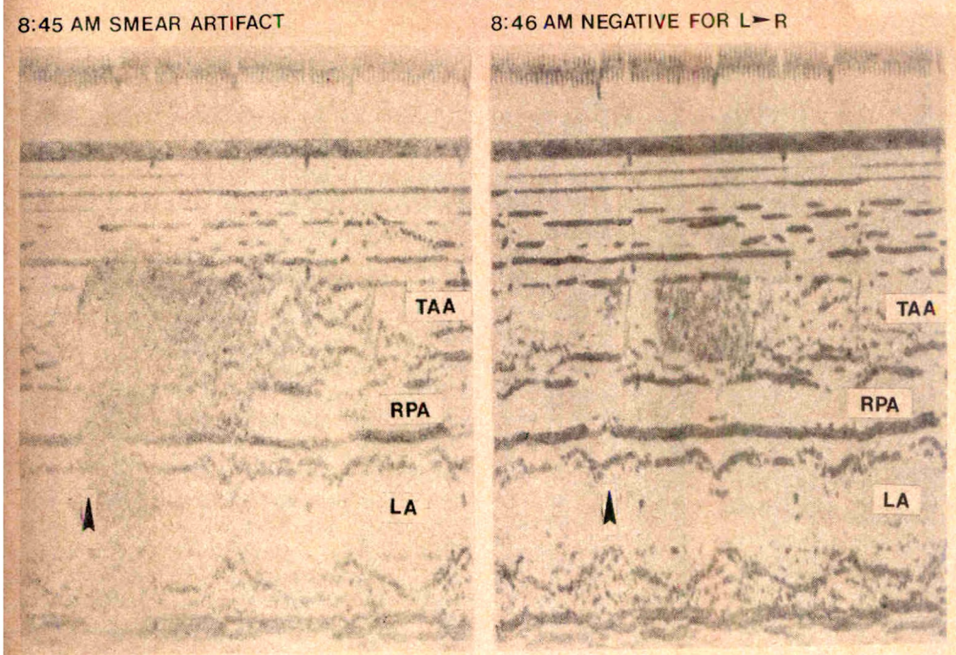


FIGURE 3. False positive "smear" artifact. **Left panel,** echo opacification traversing the entire echocardiogram. This is the result of too forceful a hand injection of contrast material. **Right panel,** an echoaortogram performed 1 minute later is negative for left to right shunting and does not show the smear artifact. **Arrows** indicate timing of injection. Abbreviations as in Figure 1.

using a 5 megahertz suprasternal transducer[9] and a commercially available echocardiograph. Echocardiograms were recorded on a continuous ultraviolet strip chart recorder. The echocardiographic "contrast" material was then hand-injected into the thoracic aorta through the umbilical arterial catheter during the recording of the suprasternal echocardiogram. Usually 1/2 to 1 cc of saline solution, dextrose in water or the patient's own blood was used as a contrast material for the echoaortogram. The maximal total amount of either saline solution or dextrose in water used was 2 cc, particularly in the smaller neonates weighing between 500 and 1,500 g. This amount usually provided four to five individual injections for evaluation. If more injections were required, the patient's blood was drawn and reinjected.

Interpretation: A left to right shunting patent ductus arteriosus was confirmed if an echocardiographic opacity was noted, not only in the transverse aortic arch but also in the right pulmonary artery (Fig. 2). The study was considered negative if the opacification occurred only in the transverse aortic arch and not in the right pulmonary artery. The injec-

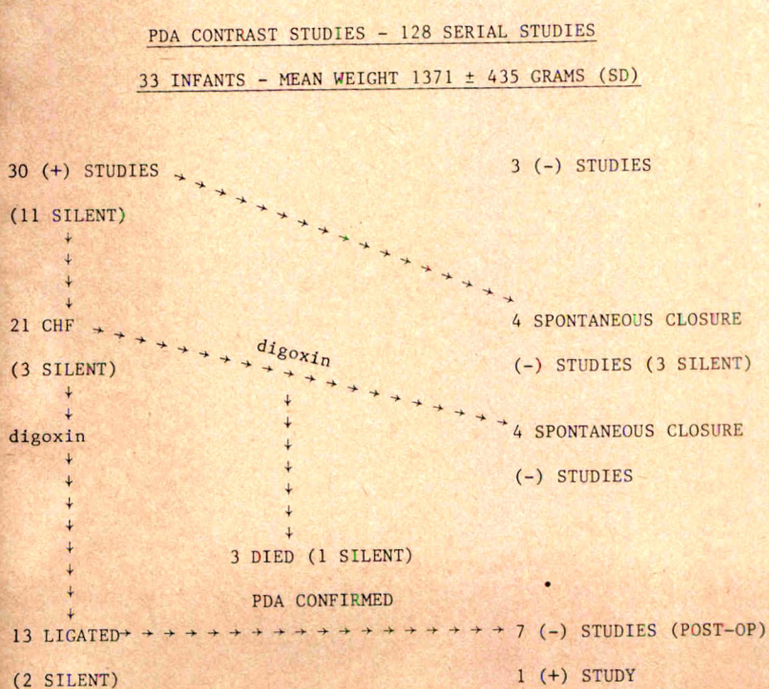


FIGURE 4. The clinical course of the patients studied. See text for details. CHF = congestive heart failure; PDA = patent ductus arteriosus; post-op = postoperative; SD = standard deviation.

tion was considered invalid if no density occurred in the transverse aortic arch or if a "smear" artifact was noted (Fig. 3). The smear artifact was easily recognizable and probably results from imaging of off-axis echoes after too forceful an injection of the contrast material. Such artifacts could be avoided by less forceful injection or an increase in the damping and reject of the instrumentation. The low gain-high reject level required for adequate lateral resolution in these small premature infants accounts for the faintness of the echocardiograms in this report. They were deliberately overexposed with high contrast technique for adequate visualization.

Results

One hundred twenty-eight serial echocardiographic contrast studies were performed in 33 consecutive patients. The mean weight of the infants was 1,371 ± 435 g (mean ± standard deviation) and their age at first study ranged from 4 hours to 9 days. All infants with catheters were prospectively studied because no parent refused consent.

Clinical course correlated with echocardiographic studies: The serial course of our patients is shown in Figure 4. Three of the 33 infants had studies negative for patent ductus arteriosus. None of these three ever had signs of patent ductus arteriosus on physical examination or in the thoracic roentgenogram, and none manifested congestive heart failure. At the time of the first study, these infants were aged 12 hours, 2 1/2 days and 1 1/2 days, respectively.

Thirty infants had positive studies. Twenty studies performed were on the first day, and 14 of these were positive for left to right ductal shunting in the first study. Twenty-four of the 30 infants with a positive study had an initially silent ductus. The ductus remained silent in 11 of these 24, including 3 who had congestive heart failure and 3 who had spontaneous ductal closure. In five symptomatic patients the patent ductus arteriosus remained open.

Of the 30 infants with a positive study 21, including the 3 who had no murmur, manifested clinical signs of congestive heart failure. All of these infants were treated with intravenously administered Lanoxin® at an average total digitalizing dose of 30 μg/kg body weight. In four patients with congestive heart failure, the patent ductus arteriosus spontaneously closed, as confirmed in subsequent negative contrast studies. Three patients with congestive heart failure died, two with murmurs and one

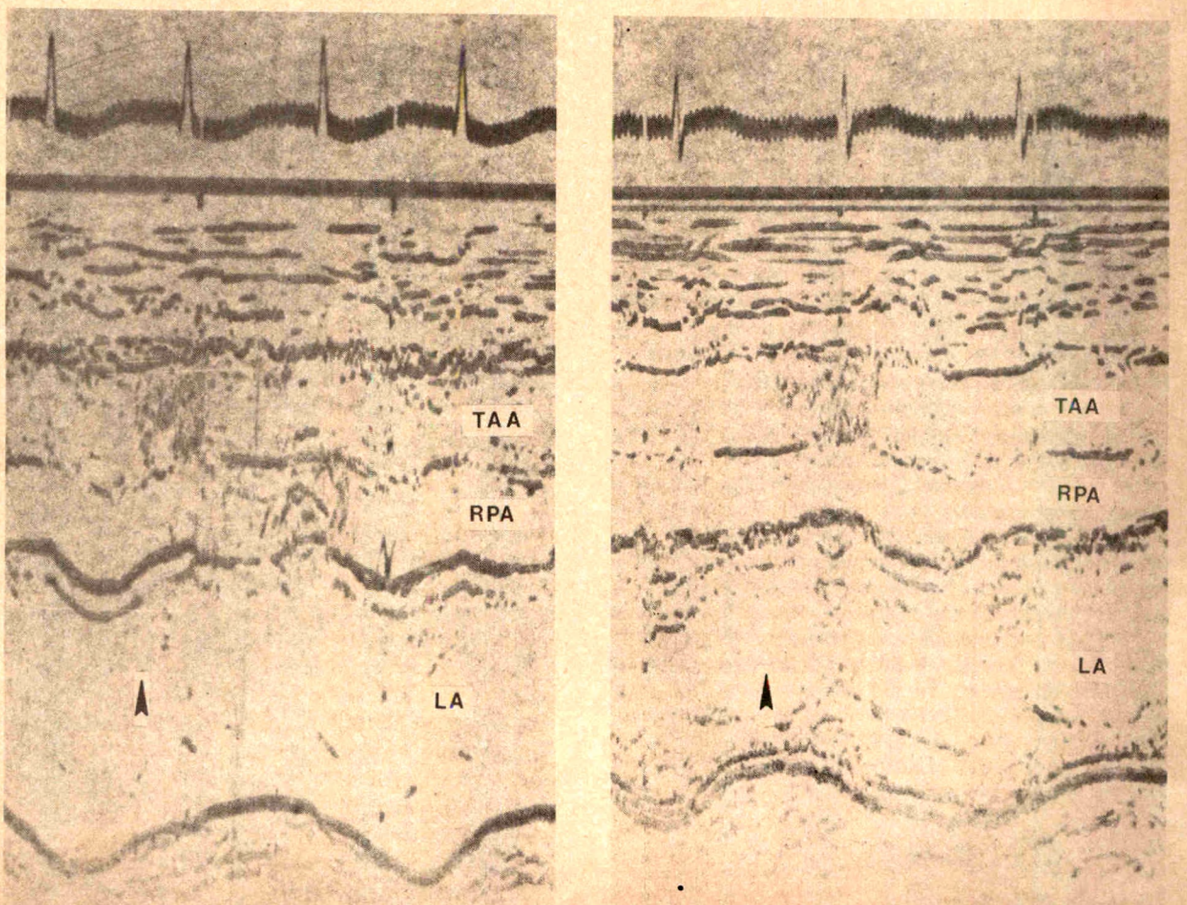


FIGURE 5. Representative serial echocardiograms of a patient who had spontaneous closure of a patent ductus arteriosus. **Left panel,** a positive study. **Right panel,** a negative study 3 days later. Note the quantitative decrease in Y′ axis left atrial size. Abbreviations as in Figure 1. **Arrows** indicate timing of injection.

with a silent patent ductus arteriosus. The cause of death was bronchopulmonary dysplasia in two of these patients and intraventricular cerebral hemorrhage in one patient. A patent ductus arteriosus was confirmed at postmortem examination in all three infants.

Patients undergoing surgical ligation of ductus: Thirteen infants did not respond to medical management and underwent surgical ligation of the patent ductus arteriosus. Two of these patients had silent patent ductus arteriosus preoperatively and throughout their course. Contrast studies performed in eight patients postoperatively revealed a negative study in seven and a positive study in one. The patient with a positive study subsequently died, and a probe patent ductus arteriosus with a slightly loose ligature around it was present at autopsy. These infants were not operated on solely on the basis of the echocardiographic data alone although the latter were combined with the thoracic roentgenographic findings and physical findings of congestive heart failure. No roentgen angiographic examinations were performed.

No complications occurred during this study as a result of the umbilical arterial catheters or the contrast technique.

Serial echoaortography: *Spontaneous closure of ductus:* Figure 5 shows serial contrast echoaortograms from a patient who had spontaneous closure of a patent ductus arteriosus. The first contrast study is positive for a left to right shunting ductus (the left panel demonstrates echocardiographic opacification of both the transverse aortic arch and right pulmonary artery). In the second study, performed 3 days later, no left to right ductal shunting is evident. The typical course for such an infant is graphically displayed in Figure 6. On the first day, when initially studied, the infant had a negative study and had no murmur or congestive heart failure. Congestive heart failure, an increased left atrial dimension and a positive contrast study were observed on the second day. A murmur was not heard until the 4th day. On the 5th day, the contrast study was negative, the murmur and congestive heart failure were gone and the left atrial dimension in the precordial echocardiogram had decreased toward normal. Four days later, before withdrawal of the umbilical arterial catheter, the left atrial dimension was still normal and the contrast study was negative.

Surgical ligation of ductus: Figure 7 shows pre- and postoperative echocardiograms from a patient who underwent ligation of a large silent patent ductus arteriosus. Before operation he had congestive heart failure (without a murmur). Serial data for a patient whose ductus was ligated are shown in Figure 8. This patient had a positive contrast study at age 8 hours and was mechanically ventilated. His contrast study remained positive throughout the rest of his course until he underwent ductal ligation. He did not have a murmur until the 5th day but had congestive heart failure requiring digitalization on the 4th day. After operative intervention the left atrial dimension returned to normal, the contrast study was negative, the murmur was gone and he had no congestive heart failure.

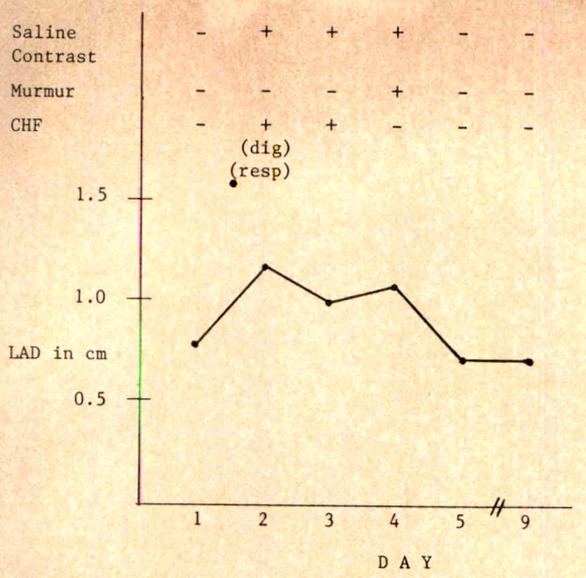
Discussion

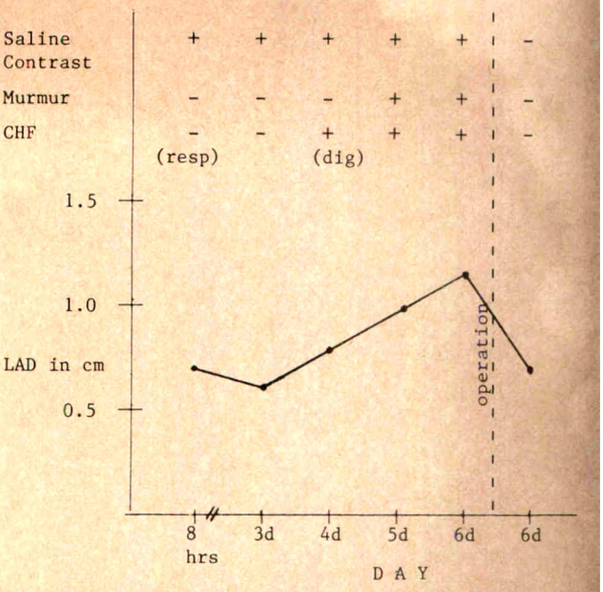
This study reports the development and validation of a reliable, safe and serially applicable bedside echocardiographic contrast technique for demonstrating a left to right shunting patent ductus arteriosus in premature infants. The technique does not require the use of angiographic contrast materials or ionizing radiation (except for initial confirmation of the location of the catheter). Nonetheless, a negative study does not mean that the duct is closed but only that a left to right shunt does not exist at the time. Echocardiography is often used in assessing the condition of infants with patent ductus arteriosus by comparing measurements of left atrial dimension, left atrial-aortic ratio or left ventricular dimension (all of which may be increased in the presence of a large left to right shunt) with standards attributing deviation from normal[14] to the effects of left to right shunts. However, standard echocardiography alone does not define the site of the left to right shunt, which might originate from a ventricular septal defect, for example. Additionally, left atrial and left ventricular enlargement can occur in premature infants as a result of fluid overload or left ventricular failure (sepsis, hypoglycemia).[8] Our contrast technique is specific for the demonstration of a left to right ductal shunt. Although the test is not quantitative, it is a sensitive qualitative detector even of small shunts.

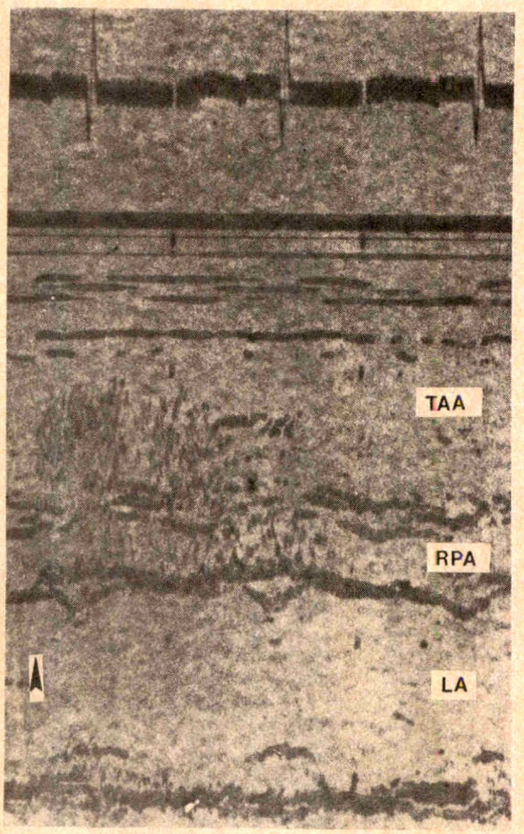
Detection of silent ductal shunt: Some large ductal shunts may be "silent" if the duct is the size of the pulmonary artery and pulmonary hypertension is present. Early detection of these shunts is important, especially when the standard echocardiogram shows unexplained left atrial enlargement. The importance of the silent patent ductus arteriosus was stressed by Thibeault et al.,[10] who reported an incidence of silent ducts similar to that of our study. The need to identify a patient with a silent ductus is evident from our finding that 3 of our 30 patients who had congestive heart failure and 2 who required operation had never had a murmur.

Advantages of serial tests: The serial application of this contrast test proved useful. The dynamics of shunting through a patent ductus arteriosus often change, and the duct can spontaneously close and reopen during the course of respiratory disease in any infant. With the catheter in place, the contrast injections can be repeated as often as necessary. This safe, simple procedure has several important uses in our neonatal intensive care nursery. It provides important differential diagnostic information for evaluating the large silent patent ductus arteriosus. Additionally, when a murmur is present but is atypical, this test confirms the presence of a patent ductus arteriosus and, in conjunction with a complete M mode echocardiographic evaluation, often helps to rule out other complicating cardiac disease. Unfortunately, no simple method yet exists for ruling out ventricular septal defect; further, this technique cannot be used to differentiate ascending aorta to pulmonary artery shunts such as truncus arteriosus or aorticopulmonary window from a patent ductus arteriosus.

Potential risks of umbilical arterial catheters: The catheter in our study was placed higher in the aorta than is the custom in many neonatal nurseries where it is usually placed below the renal arteries. Neal et al.[15] performed aortography in 19 patients with umbilical







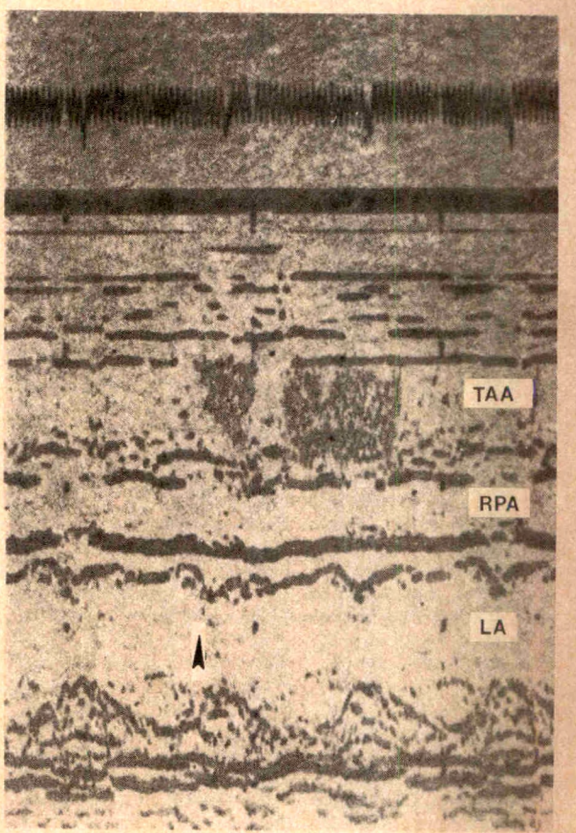


FIGURE 6 (upper left). Serial observations in a premature infant weighing 1,525 g who had spontaneous closure of a patent ductus arteriosus. Days are shown on the **abscissa.** On the **ordinate,** the **uppermost row** of plus or minus signs shows whether the saline contrast study was positive or negative. The **second row** shows whether a murmur was present or absent. The **third row** shows whether the patient had congestive heart failure (CHF). Note that the patient received digitalis (dig) and was on a respirator (resp) on the second day of life. He had no murmur. The **lowest graph** shows the Z axis left atrial dimension (LAD), in centimeters, throughout the patient's course.

FIGURE 7 (bottom). Serial echocardiograms in a patient who had a "silent" patent ductus arteriosus that required operative ligation. **Left panel,** a positive contrast study with opacification of the transverse aortic arch (TAA) and right pulmonary artery (RPA). The left atrial (LA) dimension is quantitatively enlarged. **Right panel,** taken from an echocardiogram performed 4 hours after ligation of the ductus. The contrast study is negative and the left atrial size is decreased. **Arrows** indicate timing of injection.

FIGURE 8 (upper right). Sequential data from a patient weighing 1,300 g who required ductus ligation. hrs = hours. Format and abbreviations as in Figure 6. See text for details.

arterial catheters to assess the frequency of clinically silent thromboses from the catheter. Eighteen of these patients had distinct arterial thrombus formation demonstrated by hand injection of contrast material at the time of catheter removal. Further, 12 other patients from their series died, and 7 of these had arterial clots at autopsy. Only one of these patients had clinical evidence of vascular occlusion before aortography although a second infant became symptomatic after the study. Boros et al.[16] reexamined 14 of the children who had aortograms performed by Neal et al.[15] and could not find any correlation between radiographically determined femoral or tibial length differences, pulse pressure differences or the location of the thrombi noted in the 1971 Neal aortograms. While the risk of renal involvement in catheter-associated thrombosis may exist with a high catheter location, the frequency of clotting with different catheter locations has never been systematically investigated. Other complications of umbilical arterial catheters include vessel perforation, infection, fistula, renal vein thrombosis and vasospasm.[17–19] None of these potential complications occurred in our patients. One must always weigh potential risk against potential benefit for any test. In our experience the importance of ductus identification, especially of the symptomatic silent ductus, often outweighs the potential risks of high catheter placement. The high position of the umbilical arterial catheter in our study was usually necessary for only a few days.

Implications: Echoaortography is a safe and sensitive method for demonstrating left to right ductal shunts in premature infants and is useful for serial confirmation of a left to right shunting patent ductus arteriosus. The only potential hazards are related to the safety of umbilical arterial catheters. The incidence of "silent" ductus arteriosus has been underestimated in studies that have not identified the silent ductus. Serial contrast evaluations are useful in defining the natural history of ductal shunting as an aid in the serial management of critically ill premature infants. They are clinically indicated in any premature infant with the respiratory distress syndrome who has an umbilical arterial catheter in place.

Acknowledgment

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Abnormal Right Ventricular Size and Ventricular Septal Motion After Atrial Septal Defect Closure

Etiology and Functional Significance

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Postoperative echocardiograms often demonstrate persistent right ventricular dilatation and paradoxic ventricular septal motion after repair of an atrial septal defect. To determine the prevalence, causes and significance of these echocardiographic abnormalities, 31 patients were studied with catheterization and echocardiography before and after repair of an atrial septal defect. Before operation, every patient manifested right ventricular dilatation, and all but one had abnormal septal motion. After operation, right ventricular dilatation was noted in 24 (77 percent) and abnormal septal motion in 21 (68 percent) patients despite the absence of residual left to right shunting in 30 (97 percent). These echocardiographic abnormalities could be correlated with age at operation and length of postoperative follow-up study but did not correlate with the degree of preoperative right ventricular enlargement or with shunt size or right ventricular pressure before or after operation. There was no associated functional deficit as demonstrated by the normal maximal oxygen consumption in all 13 patients who underwent treadmill exercise testing 5 to 38 months after operation; these patients included 9 with persistent right ventricular enlargement and abnormal septal motion.

Echocardiographic studies[1–4] have documented that right ventricular dilatation and abnormal motion of the ventricular septum frequently persist after operative repair of an atrial septal defect. It has been suggested that the presence of these echocardiographic abnormalities might indicate a residual left to right shunt[1,2,4] because such findings have been described as the echocardiographic hallmark of right ventricular volume overload.[2,5–7] However, because few patients have undergone postoperative cardiac catheterization the validity of this concept has not been tested. Furthermore, several recent studies[8–14] have indicated that abnormal flat or "paradoxic" septal motion can be seen in patients with right ventricular dilatation but no right ventricular volume overload.

This investigation was designed to determine whether the persistence of right ventricular dilatation and abnormal ventricular septal motion after repair of an atrial septal defect reflects persistence of interatrial left to right shunting or is related to other factors. We therefore attempted to perform hemodynamic and echocardiographic studies after operative repair of an atrial septal defect in all patients who had undergone such studies before operation at our institution.

Materials and Methods

Patients: Between September 1972 and January 1976, a total of 52 patients underwent operative repair of an isolated atrial septal defect at the National Heart, Lung, and Blood Institute. Several patients had associated anomalous pulmonary venous drainage, which was corrected at the time of repair, but no other congenital cardiac abnormalities were present. Seventeen of the 52 patients undergoing operation were not available for postoperative studies: 15 resided outside the United States, 1 had Down's syndrome and 1 was in a federal cor-

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TABLE I

Clinical, Echocardiographic, Hemodynamic and Exercise Data Before and After Repair of an Atrial Septal Defect

Case no.	Age (yr) & Sex	Defect	RVDD Index		Qp:Qs		RV Systolic Pressure		Postop Exercise Max VO_2/kg
			Pre	Post	Pre	Post	Pre	Post	
1	8M	1°	3.0	2.4	2.5:1	1:1	30	20	27.6
2	9F	1°	2.6	1.3	2.6:1	1:1	24	24	. . .
3	9F	1°	4.4	1.5	6.4:1	1:1	45	18	NM
4	10F	1°	3.2	1.3	5.6:1	1:1	50	24	. . .
5	12F	1°	1.9	0.5	4.0:1	1:1	45	51	. . .
6	17M	1°	1.6	0.8	3.8:1	1:1	26	22	. . .
7	24F	1°	2.2	1.4	2.2:1	1:1	28	24	26.6
8	66F	1°	2.0	2.1	2.3:1	1:1	35	24	22.1
9	7M	2°	3.3	2.2	3.6:1	1:1	28	24	. . .
10	8F	2°	2.4	2.1	4.4:1	1:1	28	16	. . .
11	8F	2°	3.0	2.3	1.7:1	1:1	28	28	54.1
12	8F	2°	3.2	0.8	2.2:1	1:1	32	24	28.0
13	9F	2°	3.8	1.1	4.5:1	1:1	30	28	47.2
14	9F	2°	2.5	1.6	2.3:1	1:1	34	24	. . .
15	10F	2°	2.9	1.6	8.0:1	1:1	36	22	44.8
16	16F	2°	2.4	1.7	2.2:1	1:1	28	24	. . .
17	18M	2°	2.8	1.6	3.4:1	1:1	28	18	62.9
18	19F	2°	1.6	2.3	2.4:1	1:1	55	110	. . .
19	26F	2°	2.1	1.5	2.2:1	1:1	37	90	. . .
20	27F	2°	3.2	2.1	3.5:1	1:1	29	27	28.7
21	31F	2°	2.1	1.8	2.9:1	1:1	29	18	20.8
22	34F	2°	2.9	1.7	4.0:1	1:1	36	19	. . .
23	34M	2°	1.9	1.7	1.6:1	1:1	28	20	37.4
24	37M	2°	2.1	1.8	2.3:1	1:1	26	25	. . .
25	43F	2°	2.5	2.3	2.6:1	1:1	22	22	. . .
26	45F	2°	2.5	2.2	2.7:1	1.3:1	40	38	. . .
27	51F	2°	2.5	2.3	2.5:1	1:1	23	24	. . .
28	51F	2°	2.4	2.4	3.4:1	1:1	34	27	18.7
29	58F	2°	3.0	2.4	2.8:1	1:1	45	36	. . .
30	63F	2°	3.3	2.2	1.6:1	1:1	65	45	. . .
31	63M	2°	3.1	1.6	2.2:1	1:1	45	40	23.8

ASD = atrial septal defect; 1° = ostium primum atrial septal defect; NM = not measured (because of technical difficulties); Max VO_2/kg = postoperative maximal oxygen consumption during treadmill testing (cc/min per kg); Post = postoperative; Pre = preoperative; Qp:Qs = pulmonary to systemic flow ratio; RVDD = right ventricular diastolic diameter index (cm/m^2 body surface area); RV Systolic Pressure = right ventricular peak systolic pressure (mm Hg); 2° = ostium secundum atrial septal defect.

rection institution. Of the 35 remaining patients, 33 had both cardiac catheterization and echocardiographic studies before operation. Thirty-one of these 33 patients (94 percent) also underwent complete routine postoperative echocardiographic and hemodynamic studies, and they form the basis of this report (Table I).

Age at the time of operation ranged from 7 to 66 years (median 19 years). Twenty-four patients were female and seven were male. Twenty-three patients had an ostium secundum atrial septal defect and eight had an ostium primum defect.

Hemodynamic studies: Preoperatively, all patients underwent right heart catheterization. The magnitude of left to right shunting was determined by the Fick principle from intracardiac oxygen saturation levels measured at catheterization and was expressed as the pulmonary to systemic flow ratio (Qp:Qs). Within 12 months after operation, each patient also underwent postoperative right heart catheterization. To rule out any residual left to right shunt, documentation of *both* the absence of any oxygen step-up in the right heart chambers *and* absence of any downslope break on indicator-dilution curves (pulmonary arterial injection, brachial or femoral arterial sampling) was required. In nearly two thirds of the patients, the krypton-85 shunt test was also performed to corroborate independently the absence of a residual shunt.[15]

Echocardiographic studies: Preoperative and postoperative echocardiograms were performed using a modified Ekoline 20A ultrasonic unit, a Honeywell 1856 line scan recorder, a Hewlett-Packard X-Y display, and a custom-built video amplifier. Patients were examined while recumbent and partly turned into the left lateral position. The ultrasonic transducer was placed in the third or fourth left intercostal space and the T scan technique used to locate the mitral valve tip.[16] At this level, damping and gain levels were adjusted to visualize the ventricular septum and both the right and the left ventricular free walls. Measurements from both preoperative and postoperative echocardiograms were made at or just below the level of the mitral valve tip. Right ventricular dimension, expressed as right ventricular diastolic diameter index, was measured as the distance from the right septal surface to the anterior right ventricular wall (which was assumed to be 0.5 cm posterior to the strong, nonmoving chest wall echoes)[4–6] divided by the body surface area.

Exercise testing: Fourteen consecutive patients underwent treadmill exercise testing 5 to 38 months after operative closure of the atrial septal defect. Our standard exercise protocol is described in Table II. Patients who successfully completed the standard exercise protocol rested for 30 minutes and then underwent testing under an augmented protocol, also described in Table II. The end point for both the standard and augmented exercise tests was the appearance of limiting symptoms (severe fatigue in these patients). Measurements included maximal heart rate, maximal exercise time and maximal oxygen consumption. With the patient breathing room air through a large plastic hood placed over his head, oxygen consumption was measured by means of a paramagnetic oxygen analyzer and a closed-circuit gas measuring system, as described previously.[17] Preoperative exercise tests were not performed.

Statistical analyses were performed using Student's *t* test for paired data. linear regression or the Fisher exact test, as appropriate.

TABLE II

National Institutes of Health Exercise Protocols

Time (min)	Standard Test Speed*	Standard Test Grade	Augmented Test Speed*	Augmented Test Grade
0	2.2	0%	1.9	10%
2.5	2.2	2.5%	2.3	12%
5.0	2.2	5.0%	2.7	14%
7.5	2.2	7.5%	3.1	16%
10.0	2.2	10.0%	3.5	18%
12.5	2.2	12.5%	3.9	20%
15.0	2.2	15.0%	4.7	20%
17.5	2.2	17.5%	5.5	20%
20.0	2.2	20.0%	6.3	20%
22.5	End of test	End of test	7.1	20%

* miles/hour.

Results

Prevalence of postoperative left to right shunt: In 30 of the 31 patients (97 percent), no left to right shunt at the time of postoperative catheterization could be detected with either oximetric or indicator-dilution studies (Table I). The krypton-85 shunt test was performed in 20 patients, and results were normal in all but 1 (Case 26).

Right ventricular size: Measurements of right ventricular size before and after operation are tabulated in Table I and depicted in Figure 1; mean right ventricular dimension was 2.66 cm/m^2 preoperatively and decreased to 1.75 cm/m^2 after operation (P <0.0005).

Right ventricular dilatation was present in every patient before operation; right ventricular dimension decreased after operation in 28 of the 31 patients (90 percent) (Fig. 1). In our laboratory, normal right ventricular dimension ranges from 0.6 to 1.4 cm/m^2 (mean ±2 standard deviations)[14]; thus, right ventricular size after operation was at or below the upper limit of normal in seven patients (23 percent). In two patients, right ventricular dimension was basically unchanged after operation and in one patient it was significantly greater than the preoperative value. This latter patient (Case 18) had undergone extensive pulmonary radiation therapy many years before repair of an atrial septal defect (for suspected Wilms' tumor), and marked pulmonary hypertension developed postoperatively, presumably secondary to radiation-induced pulmonary fibrosis.

Ventricular septal motion: Preoperatively, ventricular septal motion was paradoxic in 26 patients, flat in 4 and normal in 1 patient (Fig. 1). Postoperatively, septal motion was paradoxic in 14, flat in 7 and normal in 10 patients. Of the 10 patients with normal septal motion after operation, 7 had a normal right ventricular size and the remaining 3 had slight residual right ventricular dilatation.

Relation of Preoperative Factors to Postoperative Right Ventricular Size

Right ventricular size: Although right ventricular size decreased after operation in nearly all patients, preoperative right ventricular dimension did not correlate well with postoperative right ventricular size (Fig. 1). Thus, some patients with only modest right ventricular dilatation before operation continued to demonstrate modest right ventricular dilatation after operation, and several patients whose right ventricle was markedly dilated before operation demonstrated a normal or nearly normal right ventricular diameter after operation.

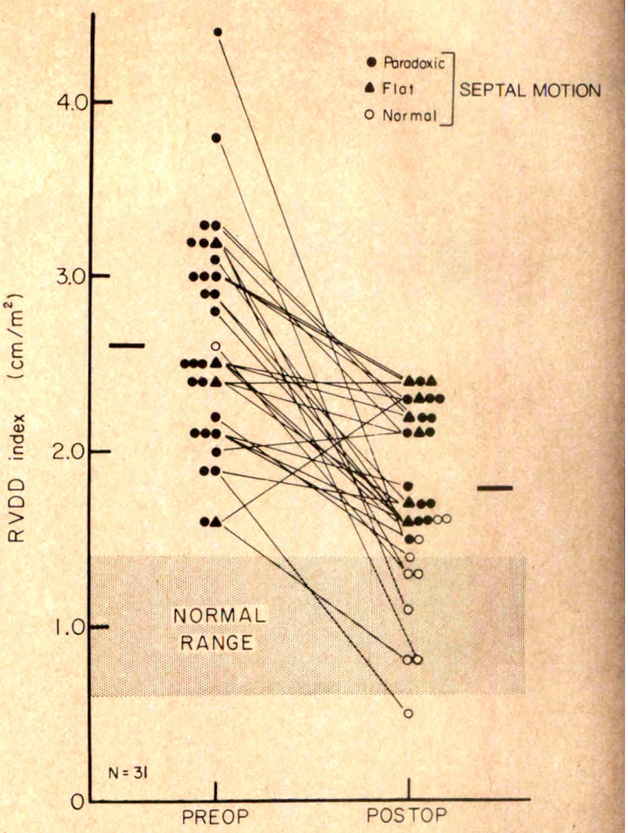

FIGURE 1. Right ventricular diastolic diameter (RVDD) index in 31 patients before (PREOP) and after (POSTOP) operative closure of an atrial septal defect. Pre- and postoperative results for individual patients are connected by **thin lines;** mean right ventricular dimension index for each group is denoted by a **bar.** For each patient, the qualitative pattern of systolic ventricular septal motion is indicated by the symbols defined at the upper right. The range for right ventricular dimension index, measured in 28 normal subjects in our laboratory,[14] is indicated by the **shaded area.** N = number of patients.

Hemodynamics: Preoperative pulmonary to systemic flow ratios ranged from 1.6 to 8.0:1 (Table I). Right ventricular dilatation was present in all patients, but the relation between preoperative pulmonary to systemic flow and preoperative right ventricular size was not strong; some patients with a relatively small shunt had marked right ventricular dilatation, whereas some with a moderately large shunt had only mild dilatation. Postoperative right ventricular dimension correlated poorly with preoperative pulmonary to systemic flow; right ventricular size returned to normal after operation in some patients who had had a large, as well as in some who had had a small, preoperative shunt.

Preoperative right ventricular peak systolic pressure was normal (30 mm Hg or less) in 16 patients and exceeded 30 mm Hg in 15 (Table I). The prevalence and

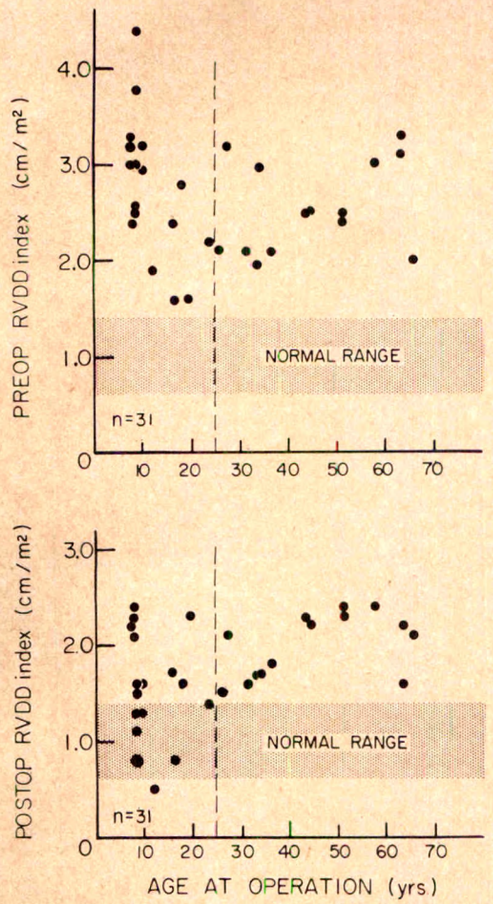

FIGURE 2. Right ventricular diastolic diameter. **Upper panel,** preoperative **(vertical axis),** related to age at the time of operation **(horizontal axis).** The **dashed vertical line** separates patients younger from those older than 25 years at the time of operation. **Bottom panel,** postoperative, same patients. The degree of right ventricular dilatation before operation is independent of the age at operation. However, normal right ventricular size after operation is observed only in those patients operated on before age 25.

degree of preoperative right ventricular dilatation were similar in both groups. Postoperative right ventricular size correlated poorly with preoperative right ventricular pressure; right ventricular dimension returned to normal after operation in some patients with normal, as well as some with elevated, preoperative right ventricular peak systolic pressure.

Age at operation: Figure 2 depicts the relation between age at the time of corrective surgery and right ventricular size. The prevalence and degree of preoperative right ventricular dilatation were equal in patients operated on before and after age 25 years. After operation, right ventricular size returned to normal in 7 of 17 patients (41 percent) operated on before age 25 years (Fig. 2). In contrast, postoperative right ventricular dimension remained abnormally increased in all 14 patients older than 25 years at the time of operation ($P < 0.05$).

Anatomy of defect: Patients with an ostium primum and those with an ostium secundum atrial septal defect demonstrated preoperative right ventricular dilatation of similar degree (Table I). Postoperative right ventricular size became normal in 5 of 8 patients (63 percent) with a primum defect but in only 2 of 23 patients (9 percent) with a secundum defect. All but one patient with a primum defect, but less than half of those with a secundum defect, were operated on before age 25 years. When only those patients who underwent repair of an atrial septal defect before age 25 were considered, postoperative right ventricular size did not return to normal in a significantly greater percent of patients with a primum than with a secundum defect.

Relation of Postoperative Factors to Postoperative Right Ventricular Size

Hemodynamics: After operation, no shunt could be detected in 30 of the 31 patients (97 percent) (Table I). Hence, postoperative right ventricular size did not correlate with the presence or absence of a persistent postoperative shunt.

Postoperative right ventricular peak systolic pressure was normal (30 mm Hg or less) in 24 patients and elevated in 7 (Table I). Right ventricular size after operation correlated poorly with the presence or absence of elevated right ventricular peak systolic pressure; although right ventricular dimension was abnormal in six of seven patients (86 percent) with persistent right ventricular hypertension, it was also abnormal in 18 of 24 patients (75 percent) with normal right ventricular pressure (difference not significant).

Duration of follow-up: The relation between the postoperative change in right ventricular size and the interval between operation and echocardiographic study is depicted in Figure 3. The magnitude of reduction in right ventricular size after repair of an atrial septal defect was not related in a linear fashion to increasing duration of the postoperative follow-up period. Large decreases in right ventricular dimension were noted in some patients studied more than 2 years after operation, but similar large decreases were also seen in patients studied in the first year after operation, including one patient studied 1 week postoperatively. Nonetheless, marked (greater than 25 percent) reduction in right ventricular size was noted in a significantly greater percent of patients studied 1 year or more after operation (12 of 14 [86 percent]) than in those studied less than 1 year after operation (6 of 17 [35 percent], $P < 0.01$). Serial postoperative echocardiographic studies were performed in four patients; two patients demonstrated continued decreases in right ventricular size, but two others had no change in right ventricular dimension.

Functional significance of postoperative right ventricular dilatation: Postoperative treadmill exercise capacity and maximal oxygen consumption were determined in 14 consecutive patients (Table I); resting right heart hemodynamics were normal in 13 (93 percent). Five patients had normal postoperative right ventricular size and normal septal motion, whereas nine had persistent right ventricular dilatation and flat or paradoxic septal motion. Regardless of the presence or

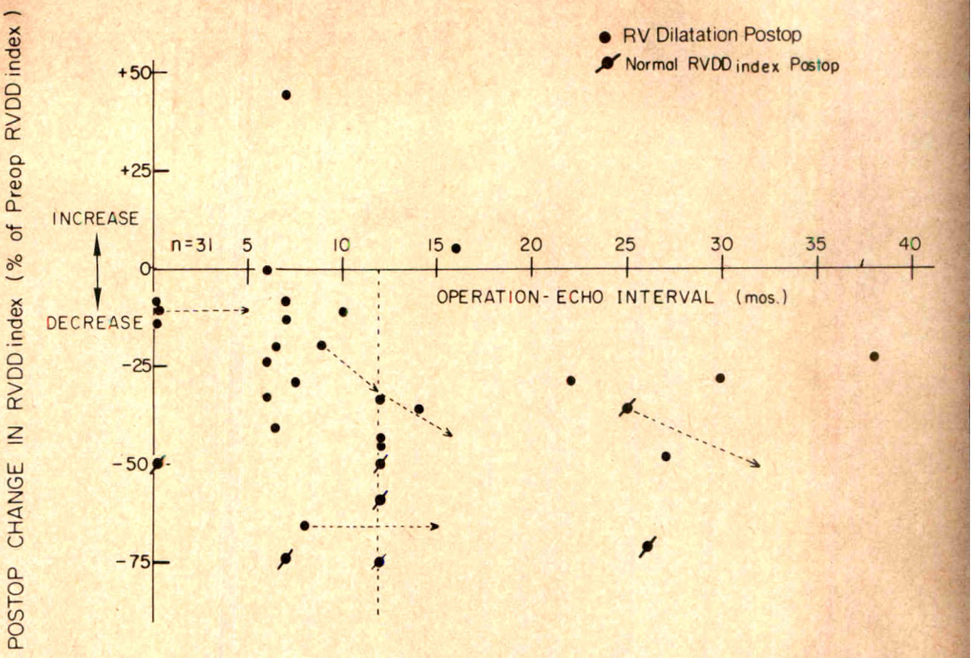

FIGURE 3. Relation between the change in right ventricular diastolic diameter (RVDD) index after operation, expressed as percent of the preoperative index **(vertical axis)** and the interval between closure of an atrial septal defect and postoperative echocardiographic study (ECHO, **horizontal axis**) in 31 patients. The **vertical dashed line** separates patients studied with echocardiography less than 1 year after operation from those studied 1 year or more after operation. Marked reductions (25 percent or more) in right ventricular (RV) size are noted in most of the latter but in less than half of the former group. n = number of patients; Postop = postoperative; Preop = preoperative.

absence of these echocardiographic abnormalities, no patient experienced dyspnea, chest pain, dizziness or arrhythmias during exercise; exercise was limited by generalized fatigue or leg fatigue. For each patient, maximal oxygen consumption during exercise was within the range previously reported[18] for apparently healthy men and women. No differences were noted between the groups with and without postoperative right ventricular dilatation.

Discussion

Our results confirm previous findings[1–4] that right ventricular dilatation and abnormal (flat or paradoxic) ventricular septal motion are often noted in the echocardiograms of patients who have undergone operative repair of an atrial septal defect. Postoperative right ventricular dilatation was observed in 24 of the 31 patients (77 percent) and abnormal septal motion in 21 (68 percent) despite the absence of a residual left to right shunt in 30 (97 percent) of the 31 patients. Thus (1) the prevalence of persistent abnormal right ventricular dilatation and abnormal ventricular septal motion after operation is great, and (2) these echocardiographic abnormalities are not indicative of incomplete closure of the atrial septal defect.

Functional significance of echocardiographic abnormalities: Maximal treadmill exercise testing in 14 patients demonstrated normal maximal oxygen consumption in all, including the 9 patients with residual right ventricular dilatation and abnormal septal motion. Because preoperative exercise tests were not performed, no conclusions can be drawn regarding any change in exercise capacity as a result of operation. Furthermore, the hemodynamic responses to intense upright exercise were not studied in these patients; hence one cannot exclude the possibility that abnormal elevations in right ventricular pressure or abnormal cardiac output responses might have been noted under conditions of stress, as previous studies from this laboratory have demonstrated.[19] Nonetheless, the normal values for resting hemodynamics and maximal oxygen consumption during exercise at the time of postoperative evaluation suggest that the persistent echocardiographic abnormalities we observed are not of important functional significance, at least over a 5 to 38 month period after operation.

Relation to residual right ventricular dilatation and overload: That echocardiographic evidence of right ventricular dilatation and paradoxic septal motion can persist after repair of an atrial septal defect in the proved absence of left to right shunt indicates that such echocardiographic abnormalities are not diagnostic of right ventricular volume overload. A recent study from our laboratory[14] of patients with normal ventricular activation and contraction demonstrated that the position of the septum within the heart at end-diastole determines both the direction and magnitude of septal motion during systole, as viewed at the level of the mitral valve tip. In that study, patients whose septum was displaced posteriorly within the heart at end-diastole (owing to right ventricular dilatation without coexisting dilatation of the left ventricle) demonstrated abnormal anterior septal motion during systole, whereas those without such posterior septal displacement (owing to lack of right ventricular dilatation or to combined right and left ventricular dilatation) demonstrated normal posterior septal motion. This observation may help to explain why patients with residual right ventricular dilatation after repair of an atrial septal defect manifest abnormal septal motion even in the absence of right ventricular volume overload. However, because of the nongeometric shape of the right ventricle, measure-

ments of right ventricular dimension can vary greatly depending on the angle at which the ultrasonic beam traverses this cavity. We have attempted to circumvent this problem,[20] as have previous workers, by performing M mode examinations in a standardized fashion and by making measurements at a precise level along the ventricular major axis. Nonetheless, distortions in right ventricular shape introduced by postoperative pericardial adhesions or cardiac rotation might alter the apparent intracardiac position of the septum and its motion during systole. Finally, abnormalities of septal motion have been reported after cardiac surgical procedures other than repair of an atrial septal defect.[21,22] Although the explanation of such abnormalities remains speculative, it is possible that intraoperative and postoperative factors, other than those discussed, may play some role in explaining the abnormalities in septal motion noted after repair of an atrial septal defect.

Factors responsible for residual right ventricular dilatation after operative repair of an atrial septal defect: The causes of such residual dilatation are probably multiple. The patient's age at the time of operation appears to correlate most strongly with the presence or absence of postoperative right ventricular dilatation. Thus, although preoperative right ventricular dilatation was equally severe in patients younger and older than 25 years at operation, right ventricular diameter returned to normal postoperatively in 41 percent of the younger patients but in none of the older group. However, other studies have shown complete resolution of right ventricular dilatation after repair of an atrial septal defect in several patients whose age was comparable with that of our older group. Nonetheless, our findings suggest that the period during which the right ventricle is dilated before operative correction exerts an important influence on the ability of the ventricle to return to normal size once relieved of its volume overload. It should be noted that patients with a primum defect constituted nearly half of our younger group but only 7 percent of our older group (Table I). Because only one patient with a primum defect underwent operation after age 25, our data cannot exclude the possibility that the anatomy of the defect, rather than age at operation in itself, might account for the greater prevalence of normal postoperative right ventricular size observed in the younger group.

The duration of the postoperative follow-up period also appears to influence postoperative right ventricular size. Continued reduction in right ventricular size in right ventricular dimension was evident in serial follow-up studies in two patients and, in general, marked reductions in right ventricular dimension were noted in a greater percent of patients studied 1 year or more after operation than in those studied less than 1 year after operation.

No strong relation was noted between right heart hemodynamics and residual right ventricular dilatation. Although postoperative elevated right ventricular peak systolic pressure was associated with postoperative right ventricular dilatation in six of seven patients, residual dilatation was also noted in 18 of 24 other patients whose postoperative right ventricular pressure was normal. In addition, the degree of preoperative right ventricular dilatation, as well as the magnitude of preoperative left to right shunt and right ventricular peak systolic pressure, correlated poorly with right ventricular size after operation. Finally, although persistence of right ventricular volume overload can cause persistent right ventricular dilatation, this influence was apparent in only one of our patients. In each of the other patients, the absence of a residual left to right shunt was established with oximetric, indicator-dilution and krypton inhalation studies. The first two techniques are sensitive indicators of hemodynamically significant left to right shunts, and the krypton shunt test uniformly detects pulmonary to systemic flow ratios as small as 1.1:1.[23]

Implications: Systematic study of patients after operative repair of an atrial septal defect indicates that most patients have residual right ventricular dilatation and abnormal ventricular septal motion even though residual left to right shunting or pulmonary hypertension is uncommon. The persistence of residual right ventricular dilatation in such instances appears to be related largely to the patient's age at operation and also to the duration of the postoperative follow-up period, but not to the degree of preoperative right ventricular dilatation, magnitude of preoperative left to right shunt, or right ventricular peak systolic pressure. Abnormalities of ventricular septal motion may be related, at least in part, to posterior displacement of the septum within the heart at end-diastole (as a consequence of right ventricular dilatation) but not to the nature of the hemodynamic burden causing such dilatation. Finally, although the presence of right ventricular dilatation and abnormal septal motion after repair of an atrial septal defect appears to have no important functional significance over a 36 month period, only long-term follow-up studies can detect whether such abnormalities will persist or be associated with an increase in late morbidity or mortality.

Acknowledgment

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Nitroglycerin-Induced Improvement in Exercise Tolerance and Hemodynamics in Patients With Chronic Rheumatic Heart Valve Disease

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Nitroglycerin reduces elevated left ventricular filling and pulmonary arterial pressures in resting patients with rheumatic valve disease and reduces symptoms when given over long periods to patients with primary myocardial disease. To determine whether nitroglycerin may prove effective therapeutically in ambulatory patients with heart valve disease, its effects on hemodynamics and exercise capacity were studied in 11 severely symptomatic adults who were already receiving optimal treatment with digitalis and diuretic agents. Seven had predominant mitral valve disease, one had predominant aortic insufficiency and three had equally severe mitral and aortic valve disease. Maximal exercise capacity was assessed with graded treadmill exercise after placebo and after nitroglycerin (0.5 mg sublingually) administered in random sequence to each patient. Exercise capacity (exercise time to limiting fatigue or dyspnea) increased from a mean of 8.3 minutes after placebo to 9.8 minutes after nitroglycerin ($P < 0.005$). Eight patients were studied hemodynamically during further intense treadmill exercise. Pulmonary arterial pressure was significantly lower ($P < 0.05$) after nitroglycerin than after placebo (mean 44 versus 56 mm Hg), but cardiac output was greater after nitroglycerin (5.0 versus 4.6 liters/min, $P < 0.005$). Thus, nitroglycerin appears to increase exercise tolerance and improve the hemodynamic response to exercise in patients with heart valve disease and may be valuable in the long-term pharmacologic therapy of such patients.

Short-term administration of vasodilators such as nitroglycerin and nitroprusside improves mechanical performance of the left ventricle at rest in patients who have acute mitral regurgitation,[1,2] chronic rheumatic heart valve disease[2,3] or chronic heart failure due to arterial hypertension[4] and those who have had an acute myocardial infarction.[5,6] Recently long-term administration of isosorbide dinitrate has been shown to reduce ventricular filling pressures measured at rest and to result in symptomatic improvement in patients with severe left ventricular failure due to primary myocardial disease.[7] However, there has been no evaluation of either objective manifestations of improved exercise performance or the effects of nitrate therapy on cardiac mechanical performance during exercise. Thus, in this investigation we assessed the effects of sublingually administered nitroglycerin on maximal exercise capacity and hemodynamics during treadmill exercise in 11 moderately to severely symptomatic adults with chronic rheumatic heart valve disease.

Methods

Patients: The 11 patients, 1 man and 10 women without prior surgical therapy, ranged in age from 25 to 71 years (Table I). From their stated histories, all had been in New York Heart Association functional class III or IV[8] for at least 6 months. Thus, all were candidates for (and subsequently underwent) surgical therapy, but none was deemed critically ill at the time of study. Each patient

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TABLE I

Patients Studied

Case no.	Age (yr) & Sex	Lesion	Rhythm
1	53F	*AR*, AS, MS	NSR
2	25F	*MR*	NSR
3	40F	*MS*, AR, TS, TR	AF
4	39F	*MS*	NSR
5	56F	MS, MR, AR, TR	AF
6	41F	*MR, MS*	AF
7	29F	AS, AR, MS, TS, TR	AF
8	68M	AR, MR	AF
9	60F	*MR*, TR, AR	AF
10	71F	*MR, MS*, AR	AF
11	47F	*MS*	NSR

Italics indicate hemodynamically predominant lesion.
AF = atrial fibrillation; AR = aortic regurgitation; AS = aortic stenosis; MR = mitral regurgitation; MS = mitral stenosis; NSR = normal sinus rhythm; TR = tricuspid regurgitation; TS = tricuspid stenosis.

was limited in activity by dyspnea or fatigue, or both. None had exercise-induced chest pain or syncope or clinical or electrocardiographic evidence of coronary artery disease. Therefore, coronary arteriography was not undertaken in these patients. All were taking digitalis and chronic diuretic therapy at the time of study. Routine diagnostic right and left heart cardiac catheterization, performed before the study, demonstrated predominant mitral valve disease in seven patients, predominant aortic regurgitation in one and significant mitral and aortic lesions in three (Table I). All patients had mitral valve disease of at least moderate severity, seven had aortic valve disease and four had tricuspid dysfunction. No patient had severe aortic stenosis or manifested wall motion abnormalities on left ventriculography.

Exercise protocol: Each patient participated in several exercise practice sessions to become familiar with the treadmill protocol. Maximal exercise capacity then was assessed in 10 of the 11 patients (at least 4 hours after the last meal) with graded upright treadmill exercise performed 3 minutes after placebo and 3 minutes after 0.4 mg of nitroglycerin, each administered sublingually in random order. The patient and the technician carrying out the study were unaware of the order in which the agents were given. The physician knew the order but remained silent so as to preclude biased exhortation of the patient. Exercise was performed at a constant speed of 2.2 miles/hour with the treadmill grade increased by 2.5 percent every 2.5 minutes. Exercise continued until the patient felt unable to proceed because of severe dyspnea or fatigue. Exercise sessions performed after placebo and nitroglycerin were separated by a 45 minute rest period.[9] No adverse effects were associated with the administration of either agent.

Hemodynamic measurements: One day after these exercise tests, eight patients were studied hemodynamically during upright treadmill exercise in order to assess the changes associated with drug administration. These 8 patients included 7 of the 10 whose maximal exercise tolerance had been tested and 1 patient who had the hemodynamic study only. Before exercise, catheters were positioned in the pulmonary and brachial arteries for measurement of pressures and for blood sampling. Total oxygen consumption was recorded continuously using a gas collection system and Beckman paramagnetic oxygen analyzer described previously.[10] Cardiac output was determined with the Fick technique.

Pressure and cardiac output determinations were made with the patient sitting upright at rest, during approximately 4 minutes of mild ("submaximal") exercise (2.2 miles/hour, 0 percent grade) and during exercise shown during previous

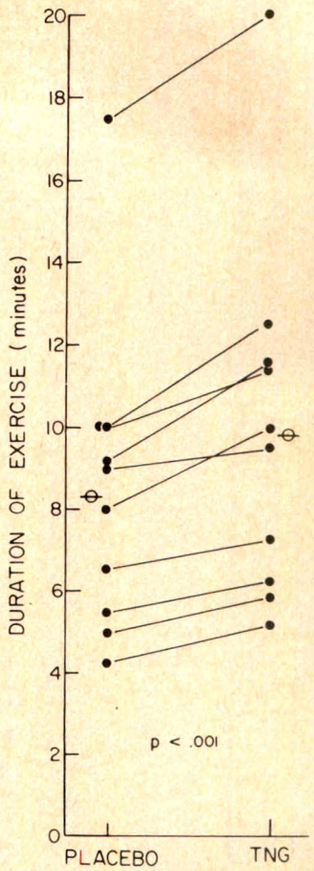

FIGURE 1. Response of exercise capacity to treatment with nitroglycerin. TNG = nitroglycerin; **open crossed circles** represent mean values for the entire group during exercise after administration of placebo and of nitroglycerin.

practice sessions to produce limiting dyspnea or fatigue after 4 minutes without nitroglycerin ("maximal exercise").[11] The higher exercise load was introduced immediately after the lower level without an intervening rest period. At each level, exercise was continued until the rate of oxygen consumption had stabilized. In all instances this occurred after 3 to 4 minutes.

After a 45 minute rest period, the exercise protocol was repeated. Exercise was begun 3 minutes after administration of placebo and 3 minutes after administration of 0.4 mg of nitroglycerin. The agents were given in random sequence and in single-blinded fashion. In all patients pulmonary arterial oxygen saturation was less than 30 percent at maximal exercise, a level previously shown to allow effective appraisal of cardiac function and separation of normal from abnormal responses to exercise.[11]

Statistical evaluations were performed with Student's *t* test and the Fisher Exact test.

Results

Exercise capacity: Exercise capacity increased with nitroglycerin in all 10 patients tested (Fig. 1). For the entire group, exercise time to limiting exhaustion or dyspnea was 8.3 minutes after placebo and increased 18 percent to 9.8 minutes after nitroglycerin ($P < 0.001$).

Heart rate and systemic arterial systolic pressure, measured by arm cuff, were indistinguishable before administration of placebo (heart rate 83 beats/min, systolic pressure 125 mm Hg) and before nitroglycerin (heart rate 86, systolic pressure 126). Within 3 minutes after administration of nitroglycerin, with the patients at rest, systemic arterial systolic pressure diminished an average of 13 mm Hg (P <0.001) and heart rate increased 14 beats/min (P <0.001). No significant alteration in either measurement was noted after administration of placebo. Despite the nitroglycerin-induced reflex increase in heart rate at rest, heart rate at the end of exercise was not significantly different after placebo and after nitroglycerin (157 versus 153 beats/min).

Hemodynamic studies: At the time of hemodynamic studies, placebo induced no change but nitroglycerin decreased systemic and pulmonary arterial pressures and increased heart rate and cardiac output (Table II, Fig. 2). During submaximal exercise after nitroglycerin, mean systemic pulmonary and arterial pressures were significantly less than during submaximal exercise after placebo, whereas cardiac output, stroke volume and heart rate were maintained at the same values (Fig. 2). More striking contrasts appeared during maximal exercise (Fig. 2 and 3). Relative to values measured during maximal exercise after placebo, prior treatment with nitroglycerin was associated with a 7 percent decrease in the systemic arterial mean pressure attained during exercise (P <0.001), a 22 percent decrease in pulmonary arterial pressure (P <0.01), a 6 percent increase in cardiac output (P <0.05) and an 11 percent increase in stroke volume (P <0.05). Heart rate during maximal exercise again was slightly lower after nitroglycerin than after placebo (153 versus 157 beats/min). However, in this phase of the study, heart rate responses during each intervention were homogeneous enough to cause the small difference to reach statistical significance (P <0.05), despite the lack of significant difference that

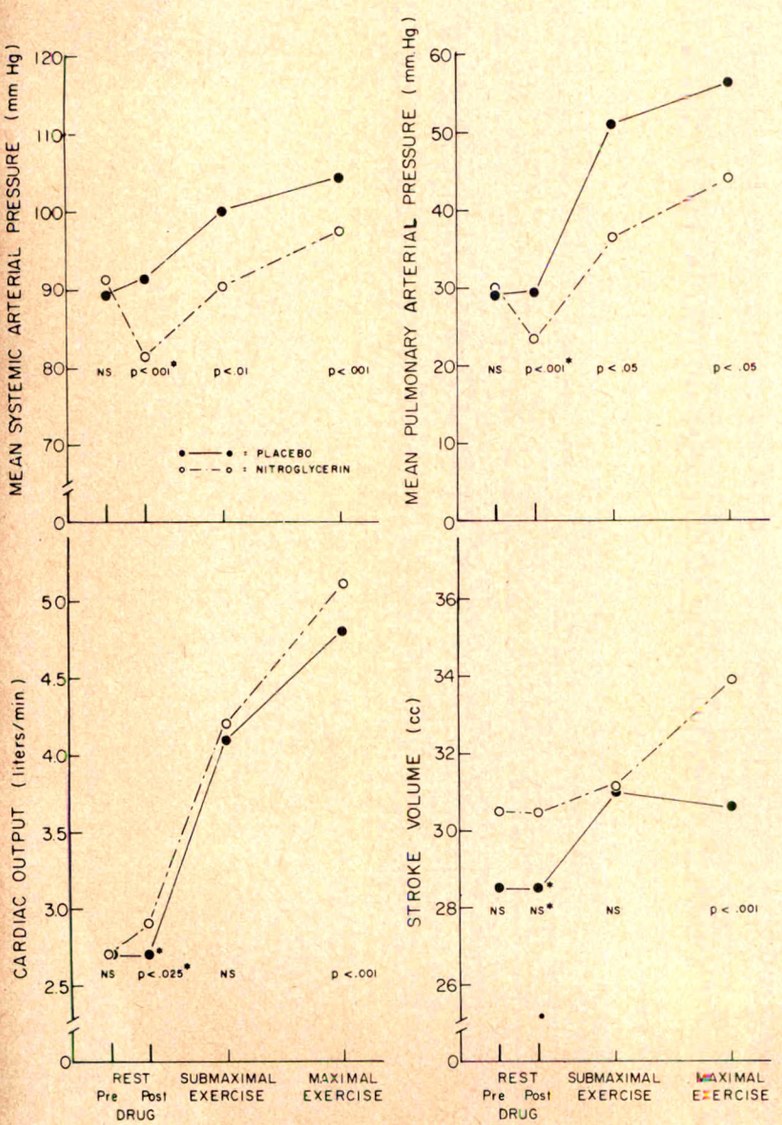

FIGURE 2. Average hemodynamic measurements at rest and during exercise after administration of placebo and of nitroglycerin: group response. *P* values with an **asterisk** refer to comparisons between hemodynamic measurements made at rest before and after nitroglycerin. No significant alterations occurred in systemic arterial or pulmonary arterial pressures at rest after administration of placebo. Cardiac output and stroke volume were not measured during rest after placebo; values noted in "Rest Post Drug" column for placebo **(closed circles with asterisks)** are the values before placebo administration. All other *P* values **(without asterisks)** refer to comparisons between measurements made after placebo and after nitroglycerin at corresponding points in the protocol. NS = not significant; Pre and Post = before and after, respectively, placebo or nitroglycerin.

TABLE II

Hemodynamic Findings During Rest

	HR	$\overline{SAP}$	$\overline{PAP}$	CO	SV
Placebo					
Before	96	90	29	2.7	29
After	96	91	29	—	—
Nitroglycerin					
Before	89	91	30	2.7	31
After	103*	82*	23*	2.9†	31

No significant differences existed in any variable in comparing values before administration of placebo and nitroglycerin.

* $P < 0.001$ when the value after nitroglycerin is compared with the value before nitroglycerin.

† $P < 0.025$ when the value after nitroglycerin is compared with the value before nitroglycerin.

CO = cardiac output (liters/min); HR = heart rate (beats/min); $\overline{PAP}$ = mean pulmonary arterial pressure (mm Hg); SAP = mean systemic arterial pressure (mm Hg); SV = stroke volume (ml).

existed when identical mean heart rates were achieved during the study of exercise capacity.

Systemic vascular resistance, estimated from cardiac output and systemic arterial pressure, decreased significantly with nitroglycerin (from 1,781 dynes sec cm^{-5} during exercise without nitroglycerin to 1,541 during exercise with nitroglycerin, $P < 0.001$). However, in this small group of patients, no relation could be found between resistance at rest or during exercise before nitroglycerin and the response of pulmonary arterial pressure, cardiac output or exercise tolerance after nitroglycerin.

Maximal oxygen consumption: Nitroglycerin did not alter total body oxygen consumption ($\dot{V}O_2$) achieved during submaximal exercise, but it produced a small but significant increase in maximal $\dot{V}O_2$. In every patient $\dot{V}O_2$ during maximal exercise was greater after nitroglycerin than after placebo (775 versus 739 ml/min, $P < 0.01$) (Fig. 4). Oxygen extraction, as measured from mean systemic arteriovenous oxygen difference, was indistinguishable after placebo (14.1 volumes percent during submaximal exercise, 15.6 during maximal exercise) and after nitroglycerin (13.7 volumes percent during submaximal exercise, 15.2 during maximal exercise).

Discussion

Our results demonstrate that nitroglycerin increases exercise capacity and improves the hemodynamic response to mild and intense upright exercise in patients with rheumatic heart disease. These beneficial effects

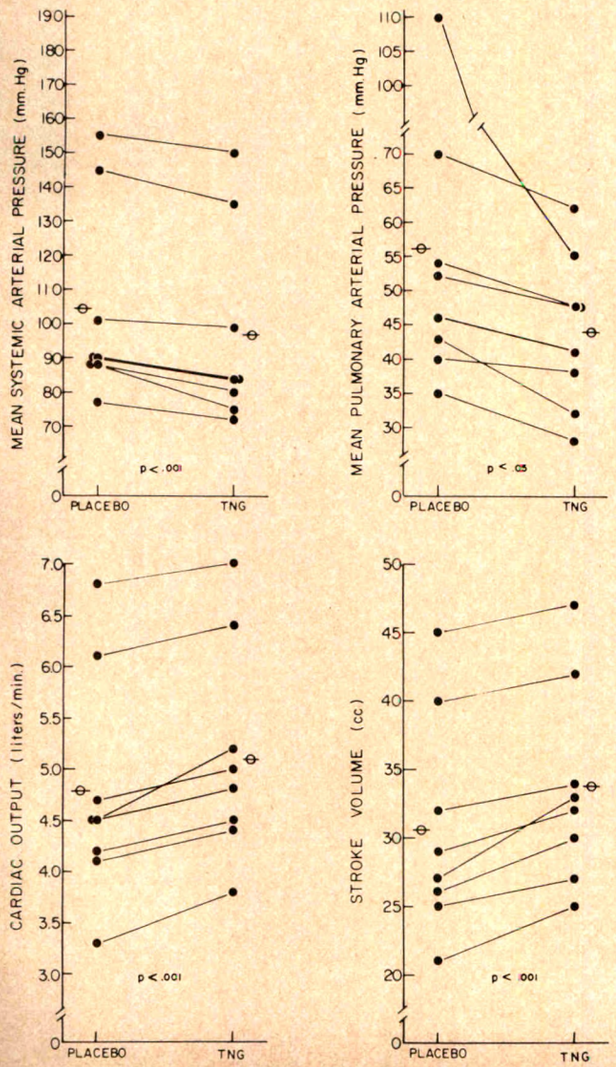

FIGURE 3. Comparison of hemodynamic measurements of "maximal exercise" after administration of placebo and of nitroglycerin: individual responses. TNG = nitroglycerin. **Open circles with bar** represent mean values for entire group.

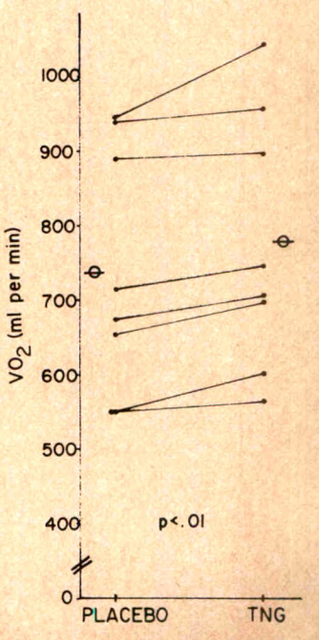

FIGURE 4. Comparison of oxygen consumption ($\dot{V}O_2$) during "maximal exercise" after administration of placebo and of nitroglycerin: individual responses. TNG = nitroglycerin. **Open circles with bar** represent mean values for entire group.

occurred in all patients studied despite their wide range of valve abnormalities. In fact, the lesions commonly involved several valves, and the results in individual patients were quite similar; thus, it is impossible to correlate particular patterns of response with specific valve lesions. Patients were already receiving optimal conventional therapy (including digitalis, diuretic agents and appropriate sodium restriction) at the time of study. Thus, the data suggest that nitroglycerin may augment functional capacity in patients with rheumatic heart disease above levels reached when only conventional treatment is employed.

Our study describes the benefits conferred during exercise by short-term administration of nitroglycerin. However, long-term administration of nitrates has produced prolonged alleviation of subjective symptoms and improvement in hemodynamics at rest in selected patients with severe myocardial dysfunction.[7] It thus seems likely that long-term administration of effective long-acting nitrate preparations will yield sustained improvement of the sort demonstrated here acutely in patients with rheumatic heart disease. However, assurance of significant benefit from long-term nitrate therapy in these patients requires further study with these agents.

Improvement in hemodynamic response after nitroglycerin included an increase in cardiac output during intense exercise and a diminution in maximal pulmonary arterial pressure. Each of those changes undoubtedly contributed to improved exercise capacity and enhanced aerobic capacity. For example, the small but significant increase in maximal oxygen consumption resulted largely from greater cardiac output during exercise because arteriovenous oxygen difference was not altered by nitroglycerin. Moreover, the reduction in pulmonary arterial pressure during exercise probably was caused, at least in part, by a decrease in pulmonary venous pressure. Such a decrease would be expected to increase static and dynamic lung compliance and reduce airway resistance.[12] The resulting reduction in the work of breathing would help attenuate or forestall exertional dyspnea and enhance exercise performance.

Mechanisms for improved hemodynamics and cardiac function: The mechanisms responsible for the nitroglycerin-mediated improvement in hemodynamics during exercise are probably related primarily to the peripheral venous and arteriolar dilatation produced by the drug.[13] Venous dilatation, by pooling blood peripherally, causes a decrease in both right and left ventricular filling pressures. The decrease in left ventricular filling pressure (and hence in pulmonary venous pressure) would diminish pulmonary vascular congestion. Whereas this mechanism is operative in all patients, undoubtedly it represents the major factor in improving exercise tolerance in patients with pure mitral stenosis. The decrease in left and right ventricular filling pressures would also diminish ventricular end-diastolic volume. This change in conjunction with the vasodilator-mediated decrease in pulmonary and systemic arterial pressures would be expected to act to decrease systolic ventricular wall stress, thus reducing myocardial oxygen consumption and enhancing systolic emptying of the ventricles.[5] At rest, this nitroglycerin-induced improvement in ventricular emptying has previously been shown to be sufficient even to preclude the decrease in cardiac output that might otherwise be expected in patients with mitral stenosis whose pulmonary arterial and left atrial pressures are reduced,[14] a finding consistent with the results of our study during exercise. Finally, in the patients with aortic and mitral valve regurgitation, the nitroglycerin-induced arteriolar dilatation and reduction in systemic vascular resistance would be expected to increase net forward cardiac output by reducing the resistance to forward flow relative to the resistance to backward flow.[1,2]

Most of the patients were premenopausal women without angina pectoris and without regional left ventricular dysfunction at rest, and it is unlikely that they had ischemic heart disease. However, occult coronary artery disease could have been present in some patients. If so, part of the nitroglycerin-mediated improvement in cardiac function during exercise might have been due to an improvement in the balance between myocardial oxygen supply and demand (perhaps in part due to improvement in coronary blood flow) with resulting reduction in ischemic dysfunction.[15]

Therapeutic implications: Our results indicate that nitroglycerin increases exercise capacity and improves circulatory function during exercise in patients with a variety of rheumatic valve lesions, even in the presence of optimal conventional medical therapy. Thus, the addition of nitrates may prove valuable and practical in the medical therapy of many patients with heart valve disease. However, we studied only the effects of an acute intervention on a small number of patients whose valve lesions were heterogeneous in nature. Thus, additional studies will be necessary to determine the efficacy of vasodilatation during exercise in groups of patients with particular types of valve lesions as well as the efficacy of long-term administration of nitrates in patients with rheumatic heart disease.

Acknowledgment

We acknowledge gratefully the valuable technical assistance of Mrs. Cora Burn, RN, Mrs. Estelle Cohen and Mrs. Joyce McKay, RN, in the performance of this study.

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Atrial Pacing for Cardioversion of Atrial Flutter In Digitalized Patients

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To test the safety and reliability of atrial pacing as a conversion technique in patients with atrial flutter who are receiving digitalis therapy, atrial pacing conversion was attempted for 49 episodes of atrial flutter in 32 consecutive patients. All patients except one were receiving digitalis. To control ventricular rates most patients had received larger than usual therapeutic doses of digitalis glycoside before pacing. Fourteen of the 25 patients whose serum levels were measured had glycoside concentrations greater than 2 ng/ml.

Before atrial pacing the mean atrial and ventricular rates were, respectively, 290 ± 20.6 and 134 ± 27.9/min (mean ± standard deviation). Successful rhythm conversion was achieved on 48 occasions (98 percent) in 31 patients. One patient required transthoracic direct current synchronized countershock cardioversion. With atrial pacing, the atrial flutter rhythm reverted immediately to sinus mechanism in 23 instances, and there were 25 episodes of atrial fibrillation. Among those who experienced atrial fibrillation, the rhythm spontaneously reverted to sinus mechanism within 24 hours on 14 occasions; on 11 occasions the rhythm reverted to atrial flutter and repeat pacing was required. Sinus mechanism was eventually established in all 31 patients.

One of the most important and promising applications of atrial pacing in recent years has been the treatment of supraventricular tachyarrhythmia, particularly atrial flutter. With pacing rates of up to 1,200/min, successful rhythm conversion to sinus mechanism has been reported in up to 80 percent (mean 59 percent) of patients with atrial flutter (Table I).

We used this technique of atrial pacing to cardiovert 49 episodes of atrial flutter in 32 consecutive patients. All but one patient had previously been treated for the rhythm disorder with large doses of digitalis to control ventricular rates. Twenty-five of the patients had also received therapeutic doses (1.2 to 1.6 g/day) of quinidine sulfate. Rhythm conversion with atrial pacing occurred on 48 occasions, and sinus rhythm was eventually established in 31 of the 32 patients. In one patient atrial pacing failed to cardiovert, and he required transthoracic direct current cardioversion.

Materials and Methods

Patients: Atrial pacing was used in 49 episodes of atrial flutter in 32 patients who failed to respond to conventional antiarrhythmic management. All of the patients were men aged 44 to 90 years (mean ± standard deviation 64 ± 10.7). Twenty patients had arteriosclerotic heart disease, two had hypertensive cardiovascular disease, four were chronic alcohol abusers and six had chronic obstructive lung disease. All 32 patients had signs and symptoms of congestive heart failure, and two complained of severe precordial chest pain. All patients except one had taken digoxin and diuretic agents, although most of them had received larger than usual therapeutic doses of the glycoside in the preceding 2 to 5 days.

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TABLE I

Analysis of Results of Major Reported Series

Reference	Pacing Episodes (no.)	Rhythm After Conversion: Sinus	Rhythm After Conversion: A Fib	Spontaneous Conversion of A Fib to Sinus Rhythm	Failure to Convert	Successful Conversions	Pacing Rates (up to) (per min)
Vergara et al.[1]	68	22	30	16	16	38	1200
Haft[2]	35	9	24	12	2	21	400
Pittman et al.[3]	26	12	12	6	2	18	800
Preston[4]	24	15	6	0	3	15	400
Zipes[5]	16	7	4	4	5	11	400
Rosen et al.[6]	15	0	6	0	9	0	600
Zeft et al.[7]	10	6	2	2	2	8	600
Gulotta and Aronson[8]	9	6	3	2	0	8	375
Cheng[9]	9	6	3	0	0	6	800
Total	212	83 (39%)	90 (42%)	42	39 (18%)	125 (59%)	

A Fib = atrial fibrillation.

Serum glycoside concentration, measured in 25 patients at the time of atrial pacing, was 2.32 ± 1.6 (mean ± standard deviation) with a range of 0.5 to 8.0 ng/ml. Fourteen patients had glycoside levels in the toxic range (greater than 2 ng/ml)[10]; no patient exhibited any ancillary signs of digitalis toxicity. One patient had acute myocardial infarction with persistent severe chest pain and signs of cardiac decompensation. He was receiving diuretics and narcotic agents; no digitalis was given to this patient. In addition, 25 patients were receiving quinidine sulfate (1.2 to 1.6 g/day) and 2 were receiving propranolol hydrochloride (40 mg/day). Mean atrial and ventricular rates in these subjects were 290 ± 20.6 (range 250 to 300) and 134 ± 27.9 (range 67 to 167) beats/min, respectively. The duration of atrial flutter ranged from 1 day to 1 year.

Atrial flutter was diagnosed with use of conventional clinical and electrocardiographic criteria. Right intraatrial electrograms, which were recorded in all patients, were required for accurate diagnosis of the tachyarrhythmia in some patients. An atrial rate of 250/min or greater was considered a prerequisite for the diagnosis of atrial flutter.

Atrial pacing: At the bedside a 4F balloon-tipped or 5F bipolar pacing probe (Elecath) was inserted percutaneously or by way of a venous cutdown into an antecubital vein and was advanced to the right atrium under continuous electrocardiographic monitoring. A prestimulation intraatrial electrogram was recorded by connecting the V lead of the electrocardiograph to the distal electrode of the catheter in all subjects. The patient was strictly isolated from all electrical circuits, and all the equipment used either had built-in electrical isolation units or was battery-operated. A standard electrocardiographic lead was monitored throughout the procedure of atrial pacing. At the termination of pacing, another intraatrial electrogram was recorded to confirm rhythm conversion. The pacing catheter was then pulled to the superior vena cava and left in place for 24 hours.

Using a square wave pulse of 2 msec duration (Med Data Inc., model MDI 100A pulse generator), atrial pacing was started at 100 impulses/min and 5 mA output. The duration of pacing varied from 2 to 30 seconds at any given rate. The pacing impulse output was gradually increased until either

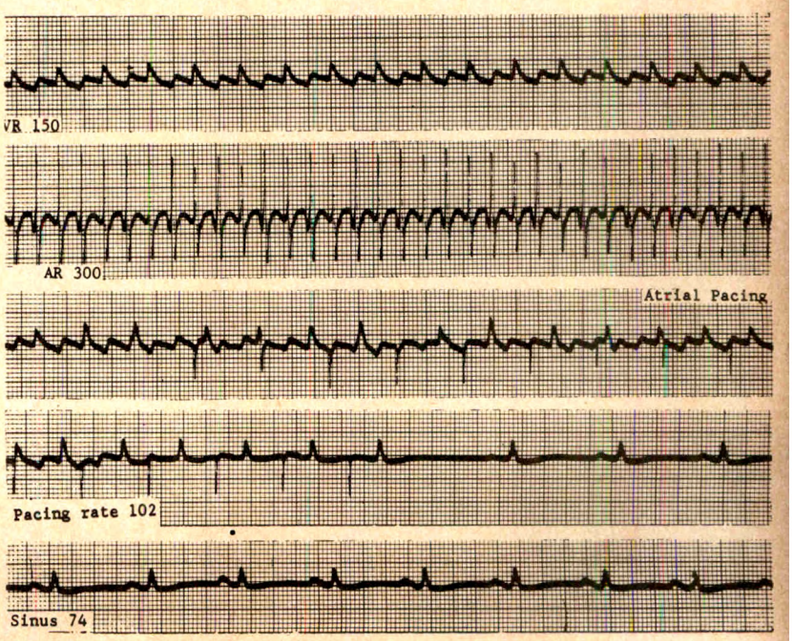

FIGURE 1. Electrocardiographic tracings recorded at the time of atrial pacing cardioversion. The **two top strips** (lead II and right atrial electrograms) reveal the rhythm to be atrial flutter with an atrial rate (AR) of 300 and a ventricular rate (VR) of 150/min. The **three bottom strips** are continuous lead II recordings revealing a pacing rate of 102 impulses/min and rhythm conversion directly to sinus mechanism at a rate of 74 beats/min.

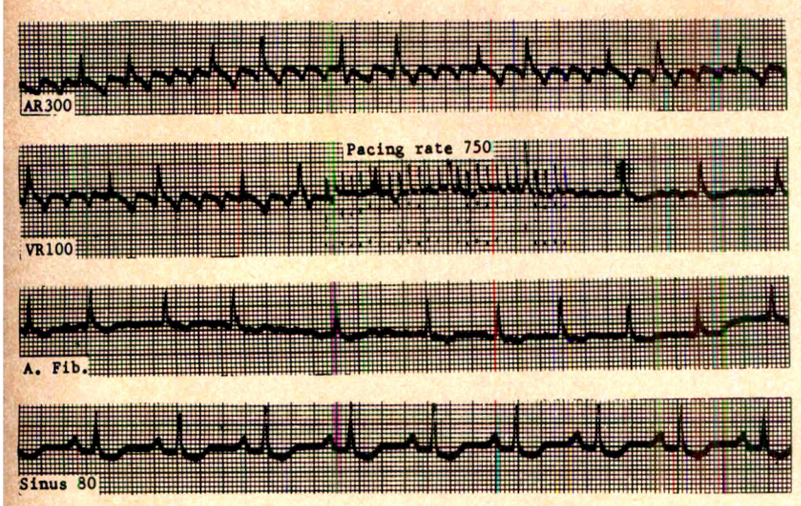

FIGURE 2. Electrocardiographic tracings recorded in a patient at the time of atrial pacing cardioversion. The **top strip** (lead II) reveals the rhythm to be atrial flutter with an atrial rate (AR) of 300 and varying ventricular response (VR) of 100/min. The **second and third strips** reveal cardioversion with atrial pacing at a rate of 750/min to atrial fibrillation (A. Fib.). Twelve hours later the atrial fibrillation converted spontaneously to sinus mechanism **(bottom strip)** at a rate of 80/min.

the rhythm was converted or a 15 mA output was reached. If cardioversion did not occur, this procedure was repeated at pacing rates of 200/min. In this manner, pacing rates were progressively increased each time by 100 impulses/min until either the rhythm was converted or a pacing rate of 1,500 impulses/min at an output of 15 mA was reached. The average pacing rate was 572 ± 453 impulses/min (range 100 to 1,500). The pulse output ranged from 5 to 15 mA (mean ± standard deviation 10 ± 2.5).

Results

Cardioversion occurred in 48 of 49 episodes (98 percent) of atrial flutter. This technique failed in one patient, who required a transthoracic direct current cardioversion. The atrial flutter converted immediately to sinus rhythm (Fig. 1) on 23 occasions (16 patients), and atrial fibrillation developed (Fig. 2) on 25 occasions (15 patients).

Twelve patients experienced early recurrence of atrial flutter (within 24 hours), but only one of these had regained sinus rhythm after atrial pacing. These 12 subjects then underwent repeat pacing. All patients who had atrial fibrillation after atrial pacing and whose rhythm did not revert back to atrial flutter had spontaneous conversion to sinus mechanism within 24 hours. In this manner sinus rhythm was established in all 31 subjects within 24 hours after atrial pacing. The mean sinus rate in these patients was 74 ± 16 (range 32 to 104 beats/min).

The immediate conversion of rhythm to atrial fibrillation was consistent throughout the range of pacing rates used. Comparison of the incidence of atrial fibrillation at pacing rates of less than 500/min to its incidence at pacing rates of 500/min or greater showed no statistical difference.

Late recurrences: Five episodes of late recurrence of atrial flutter were recorded in three patients 1 to 12 months after the initial atrial pacing cardioversion. One subject, a chronic alcohol abuser, had three late recurrences of atrial flutter on discontinuation of his medical therapy. One of the remaining two subjects had chronic obstructive lung disease, and the other had arteriosclerotic heart disease.

Postconversion bradycardia: Immediately after the rhythm conversion three patients had periods of severe sinus bradycardia (heart rate 30 to 40/min) and required cardiac pacing, which was instituted immediately by pacing the right atrium with the same pacing catheter used for pacing cardioversion. One of these three patients had persistent sinus bradycardia, and further investigation revealed a prolonged sinus recovery time. A permanent transvenous pacemaker was implanted in this patient.

Discussion

Atrial flutter frequently complicates or produces congestive heart failure, and unless the rhythm disorder is converted or the rapid ventricular rate is controlled, severe hemodynamic alterations occur, particularly in subjects with underlying myocardial disease. Cardioversion using transthoracic direct current synchronized countershock has been highly successful in terminating atrial flutter; however, its use in patients receiving large doses of digitalis can be dangerous. Several studies[11–14] have reported a high incidence rate of ventricular tachyarrhythmia in patients receiving digitalis after such cardioversion. The site of rhythm disorder in atrial tachyarrhythmia, unlike ventricular arrhythmia, is confined to the atria. Selective depolarization of atrial tissue only, which can be achieved with atrial pacing, is preferable in the management of atrial flutter and theoretically should decrease the risk of precipitating ventricular rhythm disorders.

Success rate of rapid atrial stimulation: The efficacy of rapid atrial stimulation in terminating supraventricular tachyarrhythmia (except sinus tachycardia and atrial fibrillation) has been well established.[1–5,7–9,15–17] Analysis of major reported series (Table I) reveals that this technique resulted in rhythm conversion in approximately 80 percent of the patients studied. Immediate sinus rhythm was achieved in 39 percent, but atrial fibrillation developed in 42 percent. The latter rhythm was often an unstable intermediary rhythm and usually converted spontaneously to sinus mechanism or reverted back to atrial flutter. Thus,

overall, sinus mechanism was established in 59 percent of patients, whereas rhythm conversion was not achieved in 18 percent.

In our series, at pacing rates up to 1,500 impulses/min and pacing outputs from 5 to 15 mA, rhythm conversion occurred in 98 percent of patients. The immediate postatrial pacing rhythm was sinus mechanism in 47 percent of our patients and atrial fibrillation in 53 percent. These results are comparable with those of previous reports. The atrial fibrillation after atrial pacing was an unstable intermediate cardiac rhythm converting spontaneously to sinus mechanism (in 56 percent of the patients) or reverting back to atrial flutter (in 44 percent of patients).

Recurrence rate: Early recurrence of atrial flutter (12 episodes) was confined mostly to patients in whom atrial fibrillation had been induced. The rhythm of only one subject reverted to atrial flutter after establishment of sinus rhythm. There were five episodes of late recurrence of atrial flutter in three patients. One subject had three recurrences at 3.5, 8.0 and 9.5 month intervals after the initial atrial pacing cardioversion, and in each instance the sinus rhythm was established after repeat pacing.

Mechanism for conversion with atrial pacing: The precise mechanism is not clear. A continuous movement of an impulse in atrial tissue is often thought to underlie sustained atrial flutter.[18] If this is true, a single stimulus falling in the relative refractory period and capturing the atrial tissue would interrupt the circus movement and thus abolish the flutter. The refractory periods of atrial tissue during sinus rhythm range from 150 to 360 msec.[19] However, the refractory periods of atrial tissue during atrial flutter are not known. The following mechanism is postulated to underlie the success of rapid atrial stimulation in abolishing atrial flutter: When multiple stimuli are randomly applied to atrial tissue with this technique, one or more of the stimuli fall during the relative refractory period of the atrial tissue, capturing the atrium and thus blocking advancement of the circus movement. Interruption of the atrial flutter thus allows the sinus node to resume pacemaking.

Factors affecting conversion to normal rhythm: A risk inherent in these techniques is the possibility that the stimuli may fall in the atrial vulnerable period, inducing atrial fibrillation. Because the stimuli are delivered at random, whether the rhythm converts to sinus mechanism or atrial fibrillation is also determined randomly. Indeed the incidence rates in our patients of initial rhythm conversion to atrial fibrillation (53 percent) and to sinus rhythm (47 percent) are not statistically different. The explanation for the greater incidence rate of rhythm conversion in our patients (98 percent) compared with the rate reported previously (81 percent) (Table I) is not clear. All except one of our patients were receiving digitalis, although most of them were being given larger than usual therapeutic doses of the glycoside. Digitalis abbreviates the effective refractory period and enhances the atrial conduction rate[18]; these effects may have contributed to our higher success rate. In fact, these effects of digitalis may be the mechanism by which it often abolished the atrial flutter. Another possibility is that quinidine in combination with digitalis may have provided a milieu conducive to a higher success rate for pacing-induced cardioversion.

Advantages of technique: One of the advantages of the technique of atrial pacing is that the procedure can be performed at the bedside without general anesthesia. Because we kept the catheter in the atrium for 24 hours, all of our patients who had early recurrence of atrial flutter underwent repeat pacing without additional discomfort. After rhythm conversion to sinus mechanism, three of our patients had sinus bradycardia, with rates ranging from 30 to 40 beats/min. The atrial catheter in these patients provided the means for immediate atrial pacing and control of the cardiac rate. On later investigation one of these patients was found to have an abnormally prolonged sinus nodal recovery time (sick sinus node syndrome) and required long-term transvenous pacing. Whether this patient benefited from rhythm conversion or whether he would have been better off with atrial flutter is uncertain. With this technique no ventricular arrhythmia was observed in any patient. Our results indicate that atrial pacing is a simple, highly reliable and safe technique for cardioverting atrial flutter in digitalized subjects.

Potential dangers: Although the method of atrial pacing is safe, simple and highly successful, its indiscriminate use may be dangerous. One must make certain that the catheter tip is secured high in the right atrium by repeatedly monitoring the intracavitary electrogram to avoid accidental slippage of the catheter tip into the ventricle with resulting high rate ventricular pacing and its sequelae. One must also be sure that all equipment is properly grounded to avoid the possibility of electrical leakage to the heart. Careful aseptic techniques must also be used to prevent infection and bacteremia. None of these possible complications were observed in our patients, and no patient was given prophylactic antibiotic therapy.

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Multiple Bolus Technique for Lidocaine Administration During the First Hours of an Acute Myocardial Infarction

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All patients in the San Pedro and Peninsula Hospital suspected of having a myocardial infarction are routinely given an initial bolus injection of 75 mg of lidocaine and concomitant constant infusion. Those who continue to exhibit serious ventricular ectopy are subjected to a precise treatment protocol employing 50 mg bolus injections of lidocaine every 5 minutes, if necessary, to a total of 225 mg. The clinical success of this treatment program in 1,000 consecutive patients with acute myocardial infarction prompted more extensive study of lidocaine kinetics in 23 patients receiving lidocaine with the multiple bolus technique. Plasma lidocaine levels were determined 1, 3 and 5 minutes after an initial 75 mg bolus injection and after three subsequent 50 mg bolus injections given at 5 minute intervals. The mean peak plasma concentration was 2.3 μg/ml, and no level exceeded 4.8 μg/ml. Save for a single plasma value of 1.1 μg, 5 minutes after the initial 75 mg bolus dose, the mean plasma levels were within the accepted therapeutic range at all times.

The effect of clinical left ventricular failure on plasma lidocaine levels and drug distribution was examined. Although plasma levels 1 minute after the first bolus injection were 1.0 ± 0.2 and 2.0 ± 0.4 μg/ml (mean ± standard error of the mean) in class 0–1 and class II–III heart failure, respectively ($P < 0.05$), mean concentrations were not significantly different ($P < 0.2$) 5 minutes after the last bolus dose. A dosage schedule employing multiple bolus injections of lidocaine every 5 minutes, if ventricular extrasystoles are not controlled, to a total of 225 mg over 16 minutes provides adequate blood levels, results in no significant toxicity and may be safely employed with excellent results in patients with infarction irrespective of the presence of moderate congestive heart failure.

When excessive ventricular ectopic activity occurs in the setting of acute myocardial infarction, lidocaine has been universally regarded as the treatment of choice for the prevention of sudden death due to primary ventricular fibrillation. Yet no commonly accepted standards exist to guide the clinician in administering lidocaine to the patient who has received the initial bolus injection and constant infusion but continues to have ventricular extrasystoles. The problem has been compounded because the effectiveness of lidocaine during the first hours after an infarction has been questioned.[1–4]

A protocol for the treatment of patients with acute myocardial infarction using multiple bolus injections of lidocaine when needed has been used systematically in 1,000 consecutive cases admitted to this hospital over a period of 6 years.[5] A study of the pharmacokinetics of lidocaine using the multiple bolus technique in a subset of these patients has yielded new information on the relation between the dose of lidocaine and the observed plasma levels during this early phase of treatment. This report utilizes the clinical experience from 1,000 patients with acute myocardial infarction and a subset of 23 patients with plasma lidocaine determinations to provide the data base for constructing a rational ap-

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TABLE I

Summary of Data on 1,000 Consecutive Patients with Acute Myocardial Infarction

Age (mean) (yr)	63.9 (range 27–29)
Male (%)	66
Female (%)	34
Site of infarction (%)	
Anterior	43
Inferior-posterior	41
Subendocardial	26
(9 percent of these had left bundle branch block)	
Complications (%)*	
Ventricular tachycardia	29
Shock	8.8
Congestive failure (severe)	35.3
Primary ventricular fibrillation	0.6
Mortality (%)	
Coronary care unit	9.0
Total in-hospital	11.0

* Congestive failure (severe) = presence of extensive rales or chest. X-ray evidence of advanced congestive changes; primary ventricular fibrillation = fibrillation occurring in the absence of shock or pulmonary edema; shock = systolic blood pressure of 80 mm or less for 1 or more hours accompanied by evidence of decreased peripheral perfusion and oliguria.

proach to treatment of patients who continue to have ventricular extrasystoles after the initial bolus dose of lidocaine.

Materials and Methods

One thousand patients with a definite myocardial infarction received lidocaine as dictated by a uniform protocol. These patients include 611 from the previous report of 1974[5] and 389 additional patients. If significant ventricular extrasystoles occurred after the initial 75 mg bolus injection, additional 50 mg bolus injections were given every 5 minutes if necessary to a total of 225 mg. The ventricular extrasystoles were defined as significant if they occurred on the T wave or in pairs, were multifocal or exceeded 5/min. The concomitant infusion of lidocaine (2 mg/min) was begun with the initial bolus dose of 75 mg and increased by 1 mg/min after each additional bolus injection to a maximum of 4 mg/min. If lidocaine was judged ineffective then procainamide was given intravenously in the manner previously described:[5]

Of this group, 23 patients were studied 4 to 10 days after infarction in order to determine serum lidocaine levels when the protocol was followed. The investigative nature of the study was explained and informed consent obtained in each case. An intravenous catheter was placed in one arm for the administration of lidocaine and a heparin lock inserted in the other arm for venous sampling. After the initial collection of a blank sample, a bolus injection of lidocaine was given at 5 minute intervals in the following dosages: 75, 50, 50 and 50 mg. Each individual dose of lidocaine was given as a constant rate infusion over 60 seconds; thus a total of 225 mg of lidocaine was administered in a 16 minute period.

Electrocardiographic response, cuff brachial arterial pressure, respiratory rate and central nervous system effects were monitored every 5 minutes. Venous samples to be analyzed for lidocaine concentration were obtained 1, 3 and 5 minutes after the start of each infusion. Samples were also obtained 30 and 60 minutes after the last dose. Plasma lidocaine concentration was determined using a modification of the method of Keenaghan.[6]

Left ventricular performance was classified clinically as follows: class 0, no evidence of heart failure; class I, presence of a third heart sound; class II, presence of a third heart sound and basilar rales without X-ray evidence of congestion, and class III, presence of a third heart sound, rales and X-ray evidence of congestive failure. None of the 23 patients had shock or pulmonary edema. Eleven of the 23 patients were in class II–III congestive failure. The mean body weight of the patients with class 0–1 and class II–III failure was 75.5 and 77.1 kg, respectively.

Results

Clinical Correlations

Of the 1,000 consecutive patients with an acute myocardial infarction treated over the 6 years, 315 were seen within the first hour of their symptoms and 580 within 4 hours. Thirty percent of these 1,000 patients

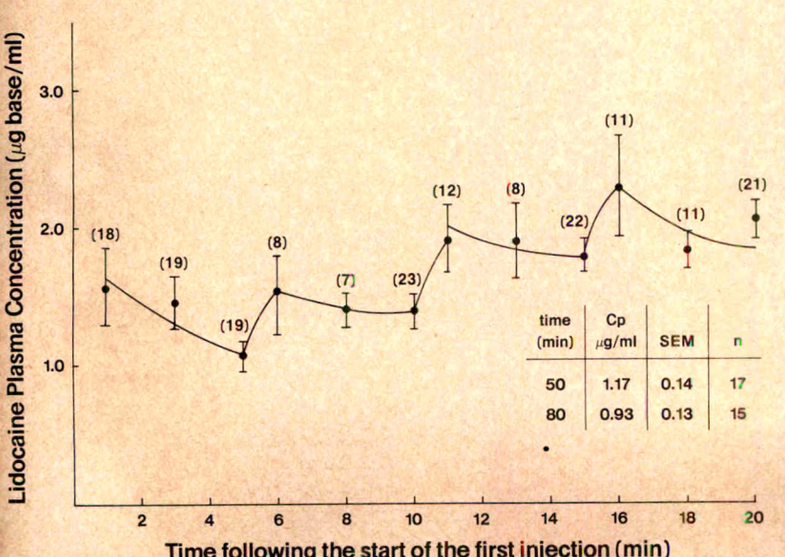

FIGURE 1. The plasma concentration-time data (mean ± standard error of the mean [SEM]) observed after administration of 225 mg of lidocaine in bolus doses every 5 minutes over a 16 minute period as described in the text. Cp = plasma concentration; n = number of plasma determinations at 50 and 80 minutes; figures in parentheses = number of plasma determinations at the times indicated.

required between two and four bolus injections of lidocaine as dictated by protocol. Eighteen percent did not respond to lidocaine and required procainamide. The average stay in the coronary care unit was 4.5 days. The clinical profile of these patients is outlined in Table I. Primary ventricular fibrillation was a rare event, occurring in 0.6 percent of patients.

Toxic and side effects: Lidocaine toxicity was confined to the central nervous system. The multiple bolus technique used during the distributions phase of the drug resulted in minor transient central nervous system side effects in less than 20 percent of the patients. These reactions included tingling and numbness of the lips and fingers. A change in hearing perception, a buzzing sound and a feeling of drowsiness were occasionally appreciated. These effects were short-lived, lasting a few minutes and in most instances were documented only by direct questioning. In one case, the infusion was discontinued after the second bolus dose because of the patient's marked lethargy. The plasma level at that time was 2.3 μg/ml. No convulsions occurred either in the subset of 23 patients or in the 1,000 patients with a proved infarction who required the multiple bolus regimen of lidocaine. Convulsions were prevented by giving the bolus no faster than 50 mg/min and by using an infusion pump during the period of continuous administration of the drug.

No adverse hemodynamic or electrophysiologic effects were encountered during this period. In particular, sinus nodal depression, atrioventricular (A-V) nodal or infranodal block did not result from this technique. No variation in the protocol was made if these abnormalities existed before the injections. One half of the prescribed dosage was given in the presence of shock or pulmonary edema.

Pharmacokinetics

Plasma lidocaine levels: In the 23 patients studied, the mean plasma levels of lidocaine observed after each dose are presented in Figure 1. These data show that the dosage schedule utilized yielded desirable drug levels. No plasma concentration greater than 4.8 μg/ml was observed; and this value is 20 percent below the usually accepted minimal toxic concentration of lidocaine (6 μg/ml). Furthermore, if 1.2 μg/ml is accepted as a minimal effective concentration, a patient exhibiting plasma levels 1 standard error of the mean below each mean plasma level would have a subtherapeutic plasma concentration only at the fifth minute following the first bolus. However, a patient with class 0–I failure is much more likely to have a subtherapeutic plasma level at these early time points than is a patient with class II–III failure (Fig. 2).

Role of heart failure: It has previously been reported that patients with heart failure (cardiac index less than 2.5 liters/min per kg and pulmonary capillary wedge pressure greater than 17 mm Hg) have a smaller initial dilution volume (V_c = Dose/C_p^0, where C_p^0 is the extrapolated zero time plasma concentration) than normal subjects.[7] In this study, we obtained all three samples after the first infusion in 15 of the 23 subjects

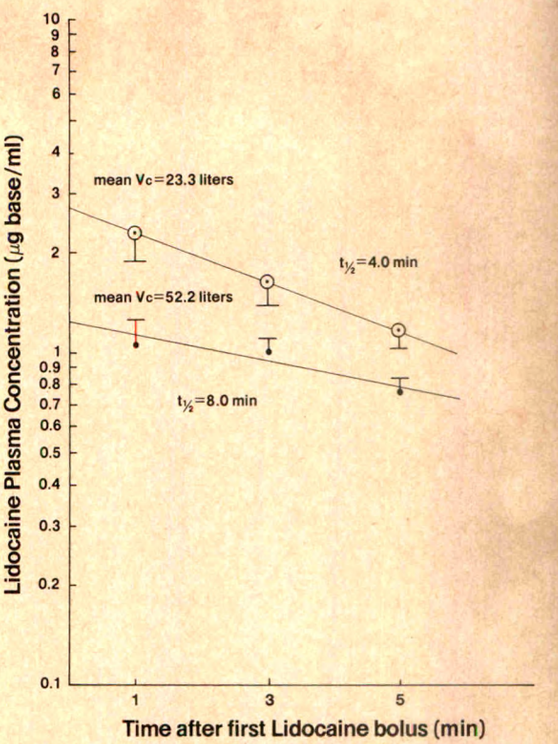

FIGURE 2. The plasma concentration-time data (mean ± standard error of the mean) observed after administration of the first lidocaine bolus dose (75 mg over 1 minute) in patients judged clinically to have class 0–1 (●) or class II–III (○) heart failure. $T\frac{1}{2}$ = half life of the initial phase of the decline in plasma concentration. Vc = initial dilution volume.

(7 with class 0–I failure and 8 with class II–III failure). Figure 2 shows that patients with failure do exhibit a substantially decreased initial dilution level (V_c)* and a decreased half-life of the initial phase of the decline of plasma concentration.† These two effects tend to compensate for one another in the multiple dose situation because in both patient populations (class 0–I and class II–III) the level of lidocaine is maintained well into the therapeutic range by the end of the second injection. At that time (6 minutes into the study), C_p in class 0–I was 1.41 μg/ml and in class II–III was 1.90 μg/ml; at the end of the second dosing interval (10 minutes into the study), these mean levels were 1.34 and

*Rigorous correction of the 1 minute infusion data to instantaneous output[11] was not practical because of our inability to adequately resolve the plasma concentration-time data into a biexponential equation with acceptable confidence limits. However, the use of reported values for the pharmacokinetic constants describing the biexponential decline of lidocaine plasma concentration suggests that the error in an extrapolation of the observed plasma levels back to zero time would cause about a 5 percent underestimate of V_c which is considered acceptable in a practical sense. Therefore the volume terms reported in Figure 2 are slight underestimates but are useful for the comparison of values among groups with various degrees of heart failure.

†This half-time is not that of the more rapid phase (that is, the alpha phase) of the biexponential decline of plasma concentration[12] but is an index of more practical importance because the value represents the time required for the initial plasma concentration of lidocaine to decrease by 50 percent.

1.55, respectively. After subsequent doses, enough drug is accumulated to bring plasma concentration further into the therapeutic range but still not close to the range where significant toxicity should be anticipated. For these reasons, a dosing scheme of the type reported here may be superior to those that rely upon a single bolus injection of lidocaine to achieve desired plasma levels.

Discussion

Is lidocaine effective?: Although lidocaine is almost universally used for the treatment of ventricular arrhythmias in acute myocardial infarction, no clear-cut guidelines have been defined for its use in the patient who has recently sustained an infarction yet continues to have ectopic ventricular rhythms after the initial bolus dose and constant infusion of lidocaine. Various investigations[1,4] have, in fact, suggested that lidocaine is ineffective against ectopic ventricular beats that occur during the first hours after infarction. A careful review of these studies reveals two unifying factors. First, the doses used were small to moderate and no blood level data were obtained from any subjects. Second, in the absence of blood level data or an indication of drug-related toxicity it seems difficult to determine if lidocaine is an inadequate antiarrhythmic agent or if the doses utilized were too small to achieve efficacious plasma levels in the majority of subjects in the study populations.[8]

Pharmacokinetics of lidocaine and clinical effects: Lidocaine is frequently used with little appreciation of the difference between the half-life during the distribution and elimination phases of the plasma concentration-time curve. When a 75 mg bolus dose of the lidocaine is injected into a peripheral vein, the drug rapidly distributes between the plasma and highly perfused tissues such as brain, lung, liver, heart and kidneys. The concentration in these organs reaches a maximum very quickly.[7] The rapid decline in plasma concentration seen in Figures 1 and 2 reflects principally the distribution of drug between these highly perfused tissues and other tissues such as muscle and fat. On the basis of previously published data,[7] the half-life of lidocaine plasma concentration during this initial time period can be calculated to be 7.3 minutes in patients with heart failure and about 8.3 minutes in normal volunteers.* In our study the half-life of lidocaine after the first bolus dose was approximately 8 minutes in patients with class 0–I failure but only 4 minutes in those with class II–III failure. The reason for our more rapid decline of plasma levels is unclear. However, all of these data strongly suggest that the clinical effect of a single bolus dose may last no longer than a few minutes.

The slower phase of lidocaine disposition kinetics (that is, the elimination phase) depends upon other factors such as the overall volume of distribution of the drug and physiologic variables such as the rate of blood flow to the liver.[9] The half-life during this phase is approximately 90 minutes, and pharmacokinetic theory predicts that it would require 5 to 7 hours of constant rate infusion of lidocaine for the plasma concentration to approach a plateau (a time when drug input equals the rate of elimination).

These two pharmacokinetic principles, the short half-life of the distribution phase and the 5 to 7 hours required to approach a plateau plasma concentration with use of constant rate infusion, could explain why some studies may have erroneously concluded that lidocaine is ineffective against ventricular ectopic activity during the first hours after infarction. Too little lidocaine has been used by the wrong method. Too often either a single bolus dose is given or alterations of the infusion rate are attempted. The former technique results in rapid distribution of the drug and consequently an inadequate blood level, whereas the latter has its effect hours later than clinically necessary. It should also be apparent that the constant infusion accompanying the initial bolus dose exerts little protective effect if ventricular extrasystoles recur within an hour after the initial dose because at the usual infusion rate of 2 mg/min only 120 mg of additional lidocaine would have been infused during the first hour. The data in our cases indicate that 225 mg given in 16 minutes results in plasma levels significantly below toxic concentrations. Specifically, the mean plasma level at the end of the last infusion was only 2.3 μg/ml.

Therapeutic implications: In the earliest stage of acute myocardial infarction the multiple bolus technique is a safe effective method of providing minimal effective blood levels tailored to each patient's needs.[10] This is shown by an incidence of primary ventricular fibrillation of less than 1 percent. Although large dose constant infusions may result in comparable blood levels with less variation, the technique does not allow for the patient whose ventricular extrasystoles will respond to a blood concentration of lidocaine lower than the so-called effective level.

Although our data confirm the observation that the initial dilution volume of lidocaine is decreased in patients with congestive failure, toxic plasma levels were not reached even in the 11 patients with moderately severe congestive failure. For patients with shock or pulmonary edema we will continue to give one-half the dose outlined in this report until further data are available.

Our study has demonstrated that 225 mg of lidocaine can be given safely in divided doses over a 16 minute period to patients with acute myocardial infarction. Despite a moderate degree of congestive failure in some patients, no toxicity occurred with this protocol.

*See preceding footnote.

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Effects of Digitalis on Sinus Nodal Function in Patients With Sick Sinus Syndrome

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The effect on sinus rhythmicity and automaticity of complete digitalization in a 24 hour period was observed in 14 patients with sick sinus syndrome. Sinus nodal function was evaluated in these patients by assessing sinus nodal recovery time and by treadmill exercise testing and 24 hour Holter monitoring, before and after digoxin administration. Corrected sinus nodal recovery times ranged from 240 to 2,065 msec (average 714) before digoxin and were shortened to 250 to 1,260 msec (average 565) after the glycoside. Further, digoxin induced accelerated infra sinus escape pacemaker activity in five patients: junctional and ventricular in one and atrial in four. Spontaneous sinus rate evaluated with Holter monitoring revealed an average of 56 beats/min (range 43 to 69) before digitalis that was unchanged (average 58 beats/min; range 48 to 74) after digoxin therapy. Similarly, the sinus nodal response to exercise was unaffected after digitalization (average 118 beats/min both before and during digitalis therapy). It is concluded that digoxin does not exert adverse effects on sinus nodal function in patients with sick sinus syndrome. The glycoside can be used safely in these patients when indicated for cardiac pump dysfunction or for control of tachyarrhythmia.

Patients with chronic idiopathic symptomatic sinus bradycardia or the "sick sinus" syndrome are frequently encountered in clinical medicine. These patients have a varied spectrum of electrocardiographic manifestations including atrial tachyarrhythmias, sinus arrest and severe sinus bradycardia.[1] If atrial tachyarrhythmia or congestive heart failure develop in these patients, the digitalis glycosides are generally considered. However, information is lacking concerning the effects of antiarrhythmic agents in general and the digitalis glycosides in particular on the function of the already diseased sinus node in patients with sick sinus syndrome. Indeed, the use of digoxin in such patients has been considered contraindicated by certain investigators.[2,3]

To clarify this issue, we undertook this study to evaluate the actions of digoxin in clinically relevant doses on sinus nodal function in patients with the sick sinus syndrome. The response of the sinus node to digoxin can be evaluated with various methods. These means of testing can be divided into certain clinically important variables such as electrocardiographic monitoring and physical exercise stress testing and recently introduced invasive measurements such as determination of sinus nodal recovery time[4,5] and sinus nodal conduction time.[6] Thus, the chronotropic effect of digoxin on the sinus node can be assessed from an extended observation period of sinus nodal rate response after digoxin administration. In addition, a stress such as that provided by treadmill testing can reveal the sinus node's ability to adapt to physiologic extrinsic or intrinsic challenges. The method of rapid atrial stimulation with measurement of sinus nodal recovery time has been utilized more recently to evaluate sinus nodal automaticity.[5,7] Therefore, in this study,

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TABLE I

Clinical and Electrophysiologic Data in 14 Patients

Case no.	Age (yr) & Sex	Cardiovascular Diagnosis	CSNRT (msec) Pre	CSNRT (msec) Post	Spontaneous Heart Rate Pre	Spontaneous Heart Rate Post	Maximal Exercise Heart Rate Pre	Maximal Exercise Heart Rate Post	Serum Digoxin Level (ng/ml)	Post Recovery and Rhythm After Atrial Pacing
1	82F	CAD	530	290	44	51	—	—	2.1	Predigoxin: SR, VR and JR with occasional prolonged J rhythm. Postdigoxin: AIVR with SR, AR and VR
2	52M	—	2,065	395	44	50	106	117	2.5	Postdigoxin: AR
3	59M	—	440	340	69	71	120	—	1.9	SR
4	70M	—	870	970	59	64	148	140	2.0	SR
5	64M	CAD	515	580	62	74	88	95	2.4	SR
6	59F	IHSS HCVD	240	260	68	74	110	—	2.3	SR
7	59F	—	780	740	72	59	—	—	2.8	SR
8	65M	CAD	500	250	48	63	100	100	2.6	SR
9	70F	HCVD	490	1,260	55	55	—	—	2.2	SR
10	67F	—	460	240	51	43	108	95	2.3	SVT precipitated frequently during atrial pacing before digoxin but not after
11	74M	CAD	440	510	52	58	138	142	2.3	Predigoxin: sinus recovery. Postdigoxin: atrial recovery at rates 130 and 140.
12	62M	CAD	90	480	48	52	152	148	1.9	Predigoxin: atrial recovery with atrial rhythm for 5 to 10 beats. Postdigoxin: same with atrial rhythm for 12 beats.
13	80F	—	2,190	480	62	58	—	—	3.4	Predigoxin: sinus recovery at rates 110 to 140. JE at 150. Postdigoxin: sinus recovery.
14*	44F	—	250	250	54	54	103	103	2.5	SR

* Corrected sinus nodal recovery time and heart rate in this patient before and after digoxin were identical.

AIVR = accelerated isorhythmic ventricular rhythm; AR = atrial recovery; CAD = coronary artery disease; CSNRT = corrected sinus nodal recovery time; HCVD = hypertensive cardiovascular disease; IHSS = idiopathic hypertrophic subaortic stenosis; J = junctional; JE = junctional escape; JR = junctional recovery; Post = after digoxin; Pre = before digoxin; SR = sinus recovery; VR = ventricular recovery.

we utilized ambulatory Holter monitoring of the electrocardiogram, treadmill exercise testing and sinus nodal recovery time determinations to quantify the effects of digoxin on sinus nodal function in patients with sick sinus syndrome.

Methods

Fourteen patients with chronic sinus bradycardia of clinically undetermined etiology presenting with such complaints as syncope, dizzy spells, lethargy, easy fatigability or palpitations were selected for this study. There were seven men and seven women ranging in age from 44 to 85 years (mean 66). Their clinical diagnoses and related investigative data are presented in Table I. Patients with very severe forms of sinus dysfunction associated with prolonged sinus arrest or persistent severe sinus bradycardia were not included in this study. Four of the 14 patients took digoxin for short intervals before the study, and the remainder were being considered for digoxin therapy. Sinus nodal function (Table II) was examined as follows: All patients underwent maximal treadmill exercise testing in the hospital. After the exercise test, 24-hour Holter monitoring was carried out utilizing the Avionics recording system. On the second in-hospital day, control sinus nodal recovery times were determined with use of intraatrial pacing,[4] after which digitalization was achieved and sinus nodal recovery time determinations, Holter monitoring and treadmill exercise testing were repeated (Table II).

Sinus nodal recovery times were measured with use of a transvenous bipolar pacing catheter advanced through the right basilic or right femoral vein and positioned high in the right atrium adjacent to the junction of the superior vena cava. Atrial pacing was then undertaken at rates ranging from 100 to 150 beats/min at increments of 10 beats/min after a full minute of pacing at each rate setting. A Medtronic temporary pacemaker (model 5880-A) was utilized and rectangular stimuli of 2 msec duration at twice diastolic threshold were used. Sinus nodal recovery times were measured after abrupt cessation of atrial pacing (Fig. 1). The recovery time was measured from the last paced P wave to the following spontaneous P wave or junctional or ventricular escape beat. Corrected sinus nodal recovery time was obtained by subtracting the prepaced control sinus cycle length (obtained by averaging three spontaneous sinus cycles immediately preceding the onset of atrial pacing) from the observed sinus node recovery time. Data were recorded on a multichannel oscilloscopic recorder (Electronics for Medicine) at a paper speed of 50 mm/sec or on a Hewlett-Packard electrocardiograph at a similar paper speed.

Digitalization: After measurement of sinus nodal recovery times, the pacing electrode was allowed to remain in the right atrium and the exteriorized portion of the wire carefully insulated and electrically isolated. The patient then received 0.03 mg/kg body weight of digoxin (range 1.5 to 2.5 mg) over the next 16 to 24 hours. The first dose of 0.25 mg was usually given intravenously and the succeeding dosages were given orally. Serum digoxin levels were obtained 6 hours after the

TABLE II

Study Protocol

Day 1	1. Treadmill test
	2. Holter monitoring
Day 2	3. Sinus nodal recovery time determination
	4. Begin digitalization
Day 3	5. Sinus nodal recovery time determination
	6. Holter monitoring
Day 4	7. Treadmill test

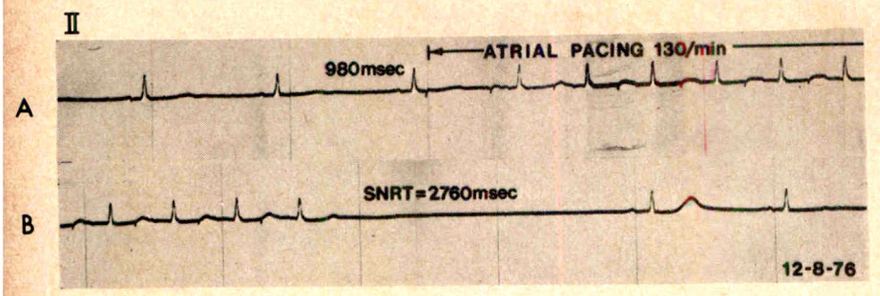

FIGURE 1. Representative example of the method for obtaining corrected sinus nodal recovery time. **A,** control sinus cycle length was 980 msec before initiation of atrial pacing (**arrow onset**) at a rate of 130/min **(top panel). B** (panels not continuous), after abrupt cessation of atrial pacing after 1 full minute, the return cycle or sinus nodal recovery time (SNRT) was measured from the last paced P wave to the first spontaneous sinus P wave (2,760 msec). The corrected sinus nodal recovery time is 1,780 msec (return cycle minus control cycle).

last oral digoxin dose and averaged 2.4 ng/ml of serum (range 1.9 to 3.4). These levels were generally higher than those at which we would prefer to maintain a patient on long-term digitalization. Sinus nodal recovery time determinations were then repeated and Holter monitoring was reinstituted. After Holter recording, the patient again underwent treadmill exercise testing while remaining on the maintenance dose of digoxin. Analysis for statistical significance in the observation before and after digoxin was evaluated by Student's paired *t* test.

Results

Sinus nodal recovery times: Results of corrected sinus nodal recovery times in the 14 patients with sick sinus syndrome before and after the administration of digoxin are depicted in Figure 2. The recovery times ranged from 240 to 2,065 msec before digoxin therapy (mean ± standard error of the mean 714 ± 179). Corrected sinus nodal recovery time was not significantly ($P > 0.05$) altered after digoxin therapy and ranged from 250 to 1,260 msec (average 565 ± 119). Sinus escape beats terminated the return cycle in 13 of 14 patients with sick sinus syndrome before digitalis therapy; but only 9 of the 14 exhibited such termination of the return cycle by sinus escape after administration of the glycoside (Fig. 1). Of the remaining five digitalized patients, one showed junctional and ventricular recovery beats, and four had atrial beats terminating the first return cycle. In these latter five patients the measured sinus nodal recovery time was an expression of the functional response of the cardiac latent automatic tissue outside the sinus node in the presence of digitalis, rather than absolute sinus nodal recovery time, and was used in computing sinus nodal recovery. In the five patients with the return cycle terminated by extrasinus beats after digoxin, the corrected sinus nodal recovery time after digoxin was not always shorter than the control measurement, and acceleration of these subsidiary pacemakers (short sinus nodal recovery time) was encountered in two patients.

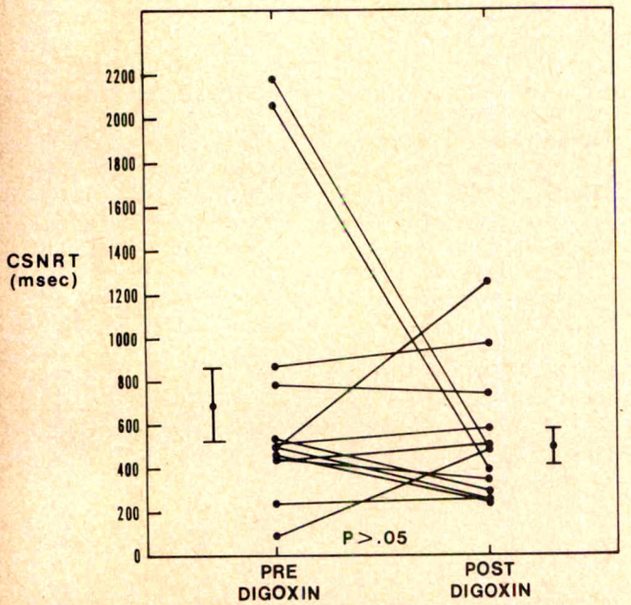

FIGURE 2. Corrected sinus nodal recovery times (CSNRT) before and after digoxin are shown for each of the 14 patients with the sick sinus syndrome. The corrected recovery time shortened in 8 of the 14 patients after digoxin and markedly so in two. Average corrected sinus nodal recovery time was 714 ± 179 msec before and 565 ± 119 after digoxin. Average corrected sinus nodal recovery time was unaltered by the glycoside ($P > 0.05$) and was increased substantially in only one patient.

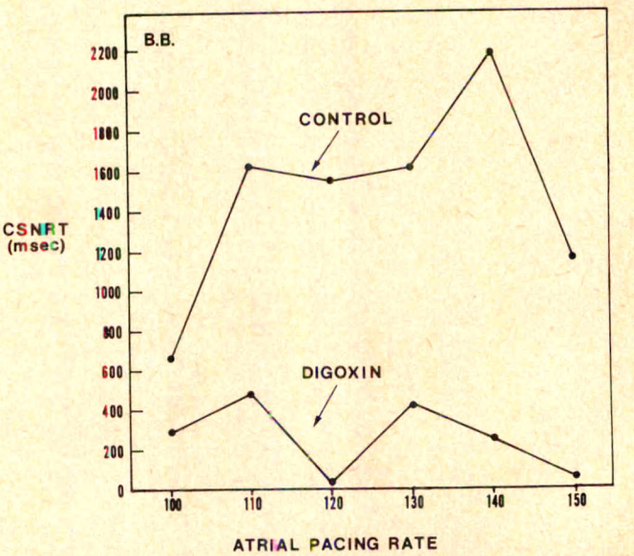

FIGURE 3. Case 13. Representative example showing corrected sinus nodal recovery time (CSNRT) as a function of atrial pacing rates. Before administration of the glycoside there was a progressive lengthening in recovery time as the atrial pacing rate was increased. In contrast, after administration of digoxin, recovery time was markedly shortened at each of the atrial pacing rates, and the maximal corrected sinus nodal recovery time was achieved at a lower rate of atrial stimulation (110/min versus 140/min before digoxin). Return cycles both before and after digitalis were terminated by sinus beats in this patient.

Case 13. A representative example of pre- and postdigoxin sinus nodal recovery times at the six pacing rates used in this patient is shown in Figure 3. At each progressively increased pacing rate from 100 to 150/min, the recovery times before digoxin administration gradually lengthened to reach a peak of 2,180 msec at the pacing rate of 140 beats/min. In striking contrast to the predigoxin recovery times, the sinus node demonstrated considerable abbreviation of corrected sinus nodal recovery time after digoxin. Thus after digoxin, the maximal recovery time achieved was 440 msec at the pacing rate of 110/min. The sinus nodal recovery times at all pacing rates after digoxin were shorter than the corresponding recovery times before drug administration, as was the case in 10 of the 14 patients. In the four patients exhibiting increased corrected sinus nodal recovery time after digoxin, the return cycle was terminated by sinus beats.

Case 1. An extreme example of corrected sinus nodal recovery time shortening induced by digoxin in this case is shown in Figure 4. The sinus node in this patient demonstrated a marked decrease of the return cycle to values less than those of the control sinus cycle at each pacing rate after administration of digoxin. The maximal control corrected sinus nodal recovery time was 530 msec but as short as −480 msec after digoxin. However, atrial pacing at a slower rate of 90/min after administration of digoxin in this patient revealed a corrected sinus nodal recovery time of 290 msec, which was considered the corrected sinus nodal recovery time in this patient.

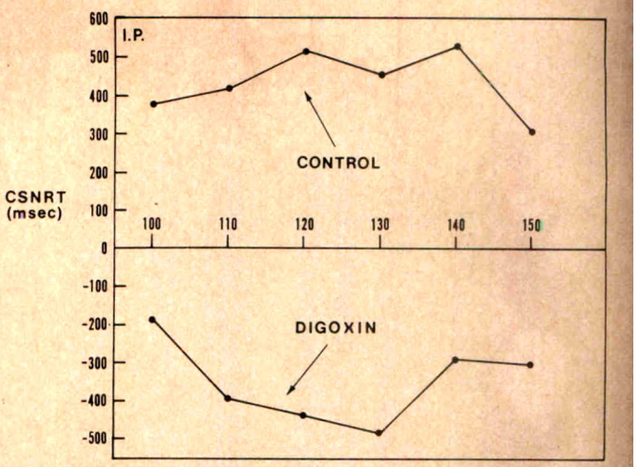

FIGURE 4. Case 1. Representative example demonstrating corrected sinus nodal recovery time (CSNRT) relative to atrial pacing rates. As in Figure 3, there was progressive lengthening of recovery time at higher atrial pacing rates. In contrast, during digoxin recovery time was strikingly shortened at each atrial pacing rate and the postdigoxin corrected recovery time values were actually negative because the return cycles were shorter than the control cycles. Again the maximal corrected recovery time was achieved at a considerably slower pacing rate after digoxin (100/min versus 140/min during the control period). In this patient, the postdigoxin escape beats were junctional in origin whereas the escape mechanism was sinus in origin before digitalis.

Ambulatory Holter monitoring: Figure 5 shows the hourly heart rates averaged for the period of Holter monitoring before and after administration of digoxin in the 14 patients. In every patient before and during digitalis therapy, averaging was achieved by determining the hourly heart rate utilizing the Avionics Holter Scanner (model 660A) for each of the 24 hours and then the hourly rates were measured and the means calculated for the individual patients. There was little or no slowing or acceleration of sinus rates in any of the 14 patients after digoxin. Each Holter tape was carefully scanned and because no substantial fluctuation of rate occurred, the frequency of sinus nodal exit block was not exacerbated by the glycoside. In no instance was supraventricular tachycardia precipitated by digitalis during the 24 hours of Holter monitoring. Control spontaneous heart rate for the 14 patients averaged 56 beats/min (range 43 to 72). Average hourly heart rates above 60 beats/min were observed in five patients. These include higher rates achieved by the patient

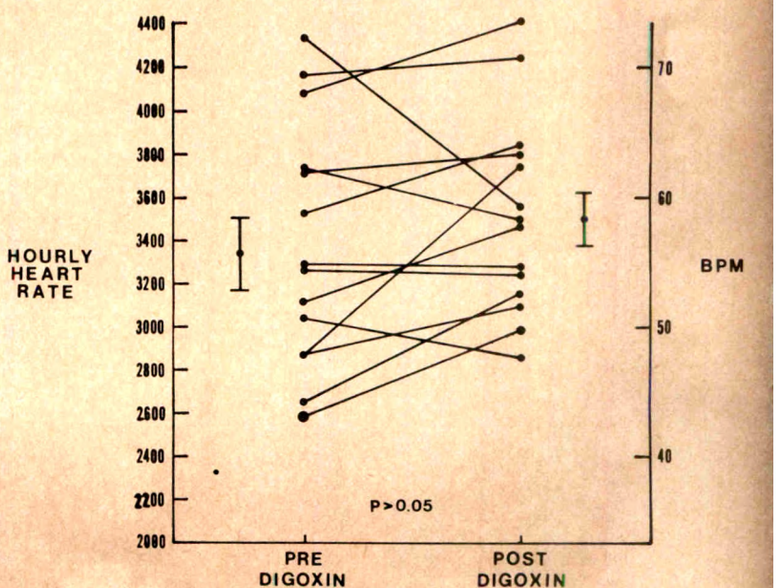

FIGURE 5. Sinus rates before and after digoxin determined from Holter monitoring in each of the 14 patients. The predigoxin heart rate (average 56 beats/min; range 43 to 72) was unaltered ($P > 0.05$) by digitalization (average 58 beats/min; range 48 to 74). The postdigoxin heart rate actually increased in 10 of the 14 patients.

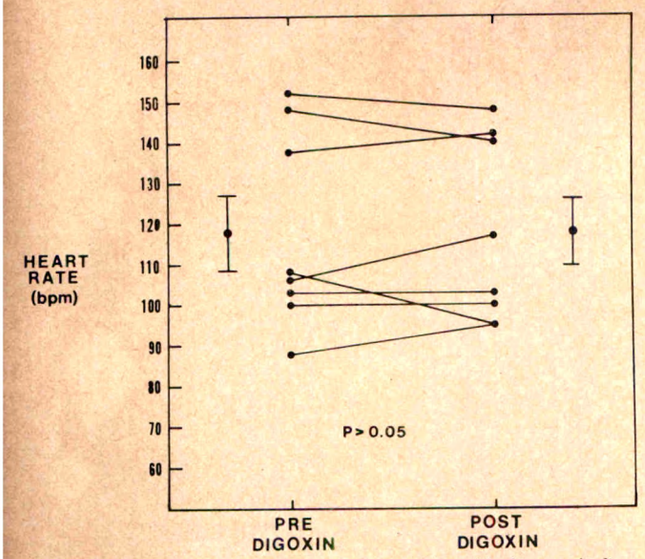

FIGURE 6. Maximal exercise heart rates achieved before and after digoxin are shown in the 14 patients with the sick sinus syndrome. Digoxin did not alter the control maximal average sinus rate of 118 beats/min ($P > 0.05$).

during daily activity. To this effect, 9 of 10 patients undergoing treadmill testing before digoxin achieved a heart rate of more than 100 beats/min. After digitalization the spontaneous heart rate was not altered ($P > 0.05$) and averaged 58 beats/min (range 48 to 74). However, a mild increase in heart rate after digoxin was observed in 10 of the 14 patients.

Sinus nodal response to exercise: Exercise testing could be performed in 8 of the 14 patients. Absolute maximal heart rate achieved during exercise was unchanged by digitalis ($P > 0.05$) (Fig. 6). Control maximal exercise heart rate averaged 118 ± 9 beats/min, and this variable was unaffected by digoxin (118 ± 8 beats/min). Control exercise duration averaged 5.12 (range 0.8 to 9.5) minutes and was similar ($P > 0.05$) after digoxin (5.92 [range 1.3 to 12.5] minutes). All patients studied had sinus rhythm before and after digoxin at rest and during exercise.

Discussion

Assessment of sinus node function in sick sinus syndrome: The normal sinus node, like other cardiac pacemakers, demonstrates the property of overdrive suppression by electrical pacemaker stimulation although the degree of such suppression is considerably less for the sinus node than for atrial, junctional and ventricular pacemakers.[8] However, it has recently been demonstrated[4] that in sick sinus syndrome the recovery response time of the diseased sinus node to overdrive suppression of the electrical pacemaker is characterized by abnormally lengthened periods of sinus standstill. This observation initiated the introduction of the commonly used test of sinus nodal recovery time for identifying the diseased sinus node. However, although sinus nodal recovery time is a useful measurement in detecting sinus nodal dysfunction, it is not definitive in this regard. Whereas Mandel et al.[4] found that 29 of 31 patients (93 percent) with the sick sinus syndrome had an abnormally prolonged sinus nodal recovery time, Gupta et al.[5] reported abnormal sinus nodal recovery time in only 6 of 17 such patients (35 percent). Rosen et al.[9] and Narula et al.[10] have reported abnormal sinus nodal recovery times in only 40 and 57 percent, respectively, of these patients. Therefore, it is clear that sinus nodal recovery time should not be used as the sole measure of sinus nodal function.

From the aforementioned observations and our clinical experience with 80 patients with the sick sinus syndrome, we now firmly believe that in the diagnosis and evaluation of sick sinus syndrome, the clinical history, Holter monitoring and pharmacologic and physiologic stresses such as atropine and exercise should constitute the adequate assessment of sinus nodal function. In this respect the only previous report[11] of the effects of a glycoside (ouabain) on sinus nodal performance in patients with the sick sinus syndrome utilized only sinus nodal recovery time for evaluation.

Sinus nodal recovery time in sick sinus syndrome: There is also lack of agreement concerning normal values for sinus nodal recovery time. Thus, some investigators[1,12] consider the total return cycle is abnormal when sinus nodal recovery time is longer than 1,400 or 1,600 msec. Further, other workers[13] use the corrected sinus nodal recovery time. Mandel et al.[4] express sinus nodal recovery time in terms of percent of the control cycle with the upper limits of normal being 115 to 128 percent. Nevertheless, the sinus nodal recovery time is a useful and valid clinical measure of sinoatrial node automaticity. Because a large number of patients with sick sinus syndrome manifest sinus arrest or marked sinus bradycardia immediately after termination of supraventricular tachycardia, atrial stimulation can simulate the phenomenon of supraventricular tachycardia. The sinus nodal recovery time and cardiac rhythmicity responses resulting after abrupt cessation of such pacing are capable of providing important information about the degree of risk of sinus arrest in these patients after suppression of the sinoatrial node. Within these advantages and limitations concerning sinus nodal recovery times, our study of corrected sinus nodal recovery times (Fig. 2 to 4) demonstrating shortening of the corrected recovery time in 10 of our 14 patients indicates that it is unlikely digoxin induces or aggravates posttachycardia asystole in patients with the sick sinus syndrome.

Effect of digitalis on sinus nodal recovery time and extrasinus pacemakers: There appear to be two reasons for shortened sinus nodal recovery time after administration of digitalis in patients with the sick sinus syndrome. The first explanation is the phenomenon of sinus nodal entrance block. Digitalis appears to induce a condition in which, at a given pacing rate, all atrial beats may not enter and depolarize the sinus node. Because sinus nodal recovery time is largely related to the atrial pacing rate, this phenomenon of entrance block protects the sinus node. It is difficult to quantitate the degree of entrance block; for example, an atrial pacing rate of 120/min may penetrate the sinus node no more than 80 times/min. Therefore, in Case 1 (Fig. 4)

the maximal recovery time obtained at the lowest pacing rate of 90/min can be explained on the basis of lack of entrance block at this lower rate.

The second explanation is that digitalis induces accelerated extrasinus pacemaker activity. The emergence of such subsidiary accelerated pacemakers in sick sinus syndrome provides another mode of functional shortening of the heart's intrinsic automatic activity rate, as shown after atrial pacing (Table I). Thus, this phenomenon of early extrasinus beats after cessation of electrical atrial stimulation during digoxin therapy occurred in two of the five patients who demonstrated ectopic recovery foci. In regard to accelerated escape rhythm, after atrial pacing or occurring spontaneously, two patients with sick sinus syndrome (Cases 1 and 12) demonstrated accelerated ventricular and atrial rhythm, respectively, in addition to escape beats. The property of digitalis of producing accelerated extrasinus escape pacemakers, as well as shortening sinus nodal recovery time, is a valuable protective mechanism against severe sinus bradycardia or asystole in patients with sick sinus syndrome. Atrial, junctional and ventricular escape beats or accelerated rhythms were independent of serum digoxin levels in our patients. The decrease in sinus nodal recovery time or generation of infranodal escape activity, or both, with digitalis therapy is shown in our study by the shift to the left of the maximal recovery time after drug therapy to a slower pacing rate, as depicted in Figures 3 and 4.

Digitalis and slowing of sinus rhythm in sick sinus node syndrome: The concept that digitalis slows sinus rhythm is the result of the observation that the agent decreases heart rate in patients with cardiac pump dysfunction and normal sinus rhythm.[14] Thus, the compensatory mechanism of augmented sympathetic discharge characteristic of the state of congestive heart failure is responsible for the relatively increased sinus rate with cardiac inotropic impairment, and the improvement in hemodynamic function after digitalis therapy allows sympathetic withdrawal and thereby a slower heart rate with the subsidence of congestive failure. Although digitalis also slightly diminishes sinus rate in normal subjects,[15] the important finding of the lack of such negative chronotropic influence on sinus function in patients with the sick sinus syndrome is demonstrated in our study and appears to be at variance with the expected observation. A possible explanation is that patients with sick sinus nodal dysfunction have impaired sympathetic activity.[16] In addition, the idiopathic fibrosis or degenerative process (or both) involving the sinoatrial node and its surrounding atrial tissue[17] is a likely contributing factor. Furthermore, the impaired response of sinus activity to physical exertion noted herein (Fig. 4) in patients with the sick sinus syndrome can also be explained on these bases. Although sinus nodal recovery time was shortened by digitalis in all of our patients, such an effect may not be universal in this condition. Thus, a single exception has been reported[18] in which sinus nodal recovery time was markedly lengthened by digoxin but sinus rate and sinus nodal conduction time were unaltered.

Therapeutic implications: From these observations obtained in our study, digoxin does not exert a detrimental action on sinus nodal performance in patients with the sick sinus syndrome at rest or during exercise. Indeed, the glycoside produces the favorable effects of decreasing sinus nodal recovery time and eliciting ectopic escape pacemakers. Therefore, digitalis is not contraindicated in the presence of the sick sinus syndrome and should be used when necessary for treatment of cardiac dysfunction.

Acknowledgment

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Effects of Morphine Sulfate on Human Coronary Blood Flow

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Because morphine causes coronary vasoconstriction in conscious dogs, human coronary blood flow was measured with the thermodilution technique before and after administration of morphine sulfate, 0.2 mg/kg body weight (maximum 15 mg) intravenously, in 10 patients to determine if the canine experience is clinically applicable. Coronary blood flow increased from a baseline value of 104.4 ± 13.4 (mean ± standard error of the mean) to 113.0 ± 17.4 ml/min (difference not significant) 15 minutes after the administration of morphine. Baseline coronary vascular resistance was 1.14 ± 0.19 mm Hg/ml/min; 15 minutes after morphine administration the resistance value was 1.02 ± 0.17 ($P < 0.025$). There was no significant change between baseline values and values 15 minutes after morphine administration in systemic mean arterial pressure (98.2 ± 5.3 to 92.8 ± 4.7 mm Hg); heart rate (69.5 ± 3.5 to 72.6 ± 3.4 beats/min), left ventricular ejection time (0.345 ± 0.009 to 0.342 ± 0.007 second) or tension-time index (2,324 ± 128 to 2,291 ± 149 mm Hg/sec per min). The slight coronary vasodilation noted after morphine administration in this study is in marked contrast to the significant coronary vasoconstriction demonstrated in the unanesthetized dog.

Morphine sulfate has been used for years to treat patients with heart disease. It is an important drug in the therapy of acute pulmonary edema due to left heart failure and is frequently used for pain relief in patients with acute myocardial infarction. A recent report[1] showed that its administration in the dog resulted in a significant reduction in coronary blood flow and an increase in coronary vascular resistance. Although clinical evidence suggests that this does not occur in man, the effect of morphine on human coronary blood flow is not known and the current study was undertaken to determine this effect.

Methods

Patients: Ten adult patients undergoing diagnostic cardiac catheterization were studied. Their diagnoses included occlusive coronary artery disease (six patients), nonocclusive coronary artery disease (two patients), pulmonary valve stenosis (one patient) and prolapse of the posterior leaflet of the mitral valve (one patient). Among the patients with coronary artery disease were six with significant (greater than 70 percent) obstruction of the luminal diameter of one or more coronary arteries, and five of these patients had significant disease of the proximal left anterior descending coronary artery. No patient had congestive heart failure. Studies were reviewed and approved by the appropriate institutional committee, and informed consent was obtained in all cases.

Procedure: Patients were taken to the cardiac catheterization laboratory without premedication after fasting for 8 hours or longer. An arterial needle was placed in the left brachial or radial artery for measurement of systemic arterial pressure with a Statham P23db strain gauge transducer and a Honeywell multichannel optical recorder with a direct writer. Systolic ejection time was calculated from arterial pressure recordings at a paper speed of 100 mm/sec. Heart rate was recorded with a simultaneous lead II electrocardiogram.

From the Division of Cardiology, Department of Medicine, The Milton S. Hershey Medical Center, Pennsylvania State University, College of Medicine, Hershey, Pennsylvania. This work was supported, in part, by grants from the South Central Pennsylvania Chapter of the American Heart Association, Harrisburg, Pennsylvania and the Sam Ostrow Cardiology Research Fund, Hershey, Pennsylvania. Manuscript received May 18, 1977; revised manuscript received August 15, 1977, accepted August 16, 1977.

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TABLE I
Hemodynamic Data in 10 Patients

Case no.	CBF		CVR		$\overline{BP}$		HR		ET		TTI		Diagnosis
	C	MS	C	MS	C	MS	C	MS	C	MS	C	MS	
1	132	223	0.68	0.42	90	94	84	82	0.28	0.29	2117	2235	Nonocclusive CAD
2	101	93	0.99	0.95	99	88	60	58	0.36	0.35	2138	1786	Mild PS
3	110	116	0.84	0.62	92	72	66	77	0.38	0.38	2307	2107	SCS
4	55	57	1.90	1.69	102	96	59	62	0.33	0.33	1986	1964	Nonocclusive CAD
5	177	188	0.52	0.48	92	90	90	90	0.34	0.34	2815	2754	CAD, RCA 100%
6	155	137	0.54	0.54	83	74	73	72	0.36	0.35	2181	1865	CAD, RCA 100%, LAD 95%, LCx 90%
7	121	97	0.78	0.97	94	94	56	58	0.35	0.34	1842	1854	CAD, LAD 100%
8	60	73	1.59	1.40	95	102	74	72	0.32	0.33	2250	2424	CAD, LAD 100%
9	69	83	1.31	1.11	91	92	71	83	0.37	0.36	2391	2749	CAD, LAD 80%, LCx 80%
10	64	63	2.27	2.00	144	126	62	72	0.36	0.35	3214	3175	CAD, LAD 80%, RCA 90%, LCx 100%

$\overline{BP}$ = mean systemic arterial blood pressure (mm Hg); C = control; CAD = occlusive coronary artery disease with 70 percent or greater stenosis; CBF = coronary blood flow (ml/min); CVR = coronary vascular resistance (mm Hg/ml per min); ET = ejection time (seconds); HR = heart rate (beats/min); LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MS = 15 minutes after administration of morphine sulfate; PS = pulmonary valve stenosis; RCA = right coronary artery; SCS = systolic click syndrome; TTI = tension-time index (mm Hg/sec per min).

A thermodilution coronary sinus catheter was introduced through a cutdown into a left antecubital vein and placed in the coronary sinus. The catheter position was verified by fluoroscopic position, injection of dye through the distal orifice of the catheter and observation of the retrograde flow and measurement of coronary sinus oxygen saturation. Once the catheter was positioned, extreme care was taken to maintain the same position throughout the study. Coronary sinus blood flow was determined with a Wilton-Webster Wheatstone bridge. Dextrose, 5 percent in water at room temperature (20° C), was injected with a Harvard constant infusion pump at the rate of 46 ml/min. Coronary flow was calculated with a modification of the method of Ganz et al.[2]

After the control measurement of coronary blood flow, heart rate, systemic arterial phasic and mean pressures and right atrial mean pressure, morphine sulfate was administered in a dose of 0.2 mg/kg intravenously (maximum 15 mg) over 2 minutes. All measurements were repeated 5, 10, 15 and 20 minutes after the administration of morphine.

Coronary vascular resistance was calculated by subtracting mean right atrial pressure from mean systemic pressure and dividing by coronary blood flow. The triple product was calculated as the product of heart rate, systolic ejection time and mean arterial pressure. Statistical analysis was performed using the Student's *t* test for paired data.[3]

Results

Mean systemic arterial pressure was 98.2 ± 5.3 mm Hg (mean ± standard error of the mean). There was a decrease 5, 10, 15 and 20 minutes after administration of morphine (91.6 ± 3.8 [$P < 0.01$] and 92.6 ± 3.3, 92.8 ± 4.7 and 93.9 ± 3.9 mm Hg, respectively) (differences not significant).

Control ejection time was 0.345 ± 0.009 second. There were nonsignificant changes 5, 10, 15 and 20 minutes after morphine administration (0.344 ± 0.009, 0.341 ± 0.008, 0.342 ± 0.007 and 0.346 ± 0.008 second, respectively).

Control heart rate was 69.5 ± 3.5 beats/min. There were nonsignificant increases 5, 10 and 15 minutes after morphine administration (71.3 ± 2.4, 71.5 ± 2.7 and 72.6 ± 3.4, respectively) and a nonsignificant decrease to 68.2 ± 4.0 beats/min at 20 minutes.

Control tension-time index was 2,324 ± 128 mm Hg/sec per min. There were nonsignificant decreases 5, 10, 15 and 20 minutes after morphine administration (2,236 ± 110, 2,250 ± 114, 2,291 ± 149 and 2,169 ± 83 mm Hg/sec per min, respectively).

Control coronary blood flow was 104.4 ± 13.4 (range 55 to 177) ml/min. There were nonsignificant increases in flow 5, 10, 15 and 20 minutes after morphine administration (109.0 ± 14.1, 112.4 ± 16.6, 113.0 ± 17.4 and 106.3 ± 14.9 ml/min, respectively). Control coronary vascular resistance was 1.14 ± 0.09 mm Hg/ml per min. At 5, 10, 15 and 20 minutes after morphine administration, resistance had decreased to 1.01 ± 0.16 ($P < 0.005$), 1.03 ± 0.18 ($P < 0.05$), 1.02 ± 0.17 ($P < 0.025$) and 1.08 ± 0.18 mm Hg/ml per min (differences not significant), respectively.

Patients with and without coronary artery disease: Individual data for the control period and 15 minutes after morphine administration are presented in Table I. The four patients without coronary artery disease had a baseline coronary blood flow value of 99.5 ± 16.2 ml/min; 15 minutes after morphine administration blood flow increased to 122.2 ± 35.7. The six patients with occlusive coronary artery disease had a baseline coronary blood flow value of 107.7 ± 20.7 ml/min; 15 minutes after morphine blood flow was 106.8 ± 19.3. Thus the patients with normal coronary arteries had a mild increase in coronary blood flow after morphine, whereas those with coronary artery disease showed no change.

The four patients without coronary artery disease had a control coronary vascular resistance level of 1.18 ± 0.27 mm Hg/ml per min; 15 minutes after morphine administration resistance had decreased to 0.92 ± 0.28. The six patients with occlusive coronary artery disease had a control coronary vascular resistance value of 1.17 ± 0.28 mm Hg/ml/min; 15 minutes after morphine resistance had decreased to 1.08 ± 0.23. Thus both groups of patients showed a similar decrease in coronary vascular resistance.

Discussion

Morphine sulfate is a "first line" drug in the therapy of acute pulmonary edema secondary to left heart fail-

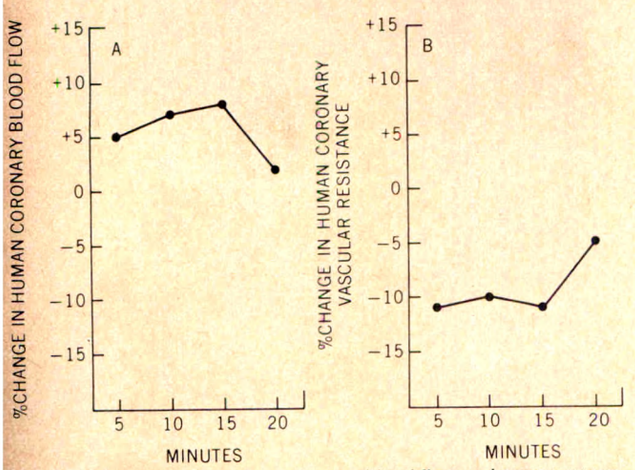

FIGURE 1. Percent change in coronary blood flow and coronary vascular resistance in 10 cases 5, 10, 15 and 20 minutes after administration of morphine.

ure.[4] It is also frequently used for pain relief in the patient with acute myocardial infarction. Clinical experience suggests that no major adverse cardiac effects occur when this drug is properly used in the patient with cardiac disease. However, recent data show an increase in coronary vascular resistance and a decrease in coronary blood flow after its administration in dogs.

Vatner et al.[1] showed a 28 percent decrease in canine coronary blood flow and a 31 percent increase in coronary vascular resistance 15 minutes after morphine administration. Similar results in man would significantly alter management of the patient with acute cardiac disease. In contrast to the canine study, our findings in patients revealed a minimal (8 percent) increase in coronary blood flow and a significant (11 percent) decrease in coronary vascular resistance 15 minutes after morphine administration (Fig. 1). Therefore in human beings morphine does not constrict the coronary arteries.

Reason for the differences between effects of morphine in canine and human studies: The reason for these differences is not completely apparent. In the dog, the predominant dose of morphine was 2.0 mg/kg body weight, whereas we used 0.2 mg/kg. However, in the dog, coronary vasoconstriction of a lesser magnitude was also demonstrated with a dose of 0.25 mg/kg. A species difference rather than a difference in dose is a more likely explanation for the different responses of the coronary bed to morphine. Whereas the mechanism of the coronary vasoconstriction in dogs is increased alpha adrenergic tone, in man, a reduction in vascular alpha adrenergic tone has been shown, at least in the limb circulation.[5]

Our indirect indexes indicated an apparent nonsignificant decrease in myocardial oxygen needs. There was a slight decrease in systemic mean arterial pressure (5 percent), systolic ejection time (1 percent) and tension-time index (1 percent). Although there was a slight increase in heart rate (3.1 beats/min) at 15 minutes, this was probably not enough to offset the other factors that would decrease myocardial oxygen requirements. The nonsignificant reduction in arterial pressure was probably too slight to permit one to postulate an autoregulatory mechanism for the observed coronary vasodilation. Thus, the reason for the decrease in coronary vascular resistance is not apparent from our study.

Therapeutic implications: The clinical conclusions of our study are clear. Unlike dogs, patients, including those with coronary artery disease, do not respond to morphine administration with constriction of coronary vessels. Because morphine did not significantly alter myocardial oxygen requirements or coronary blood flow, one can conclude that physicians should continue to use morphine as they have in the past to treat appropriate patients with heart disease. As has been proved by countless years of clinical experience, morphine is a safe drug in such patients.

Acknowledgment

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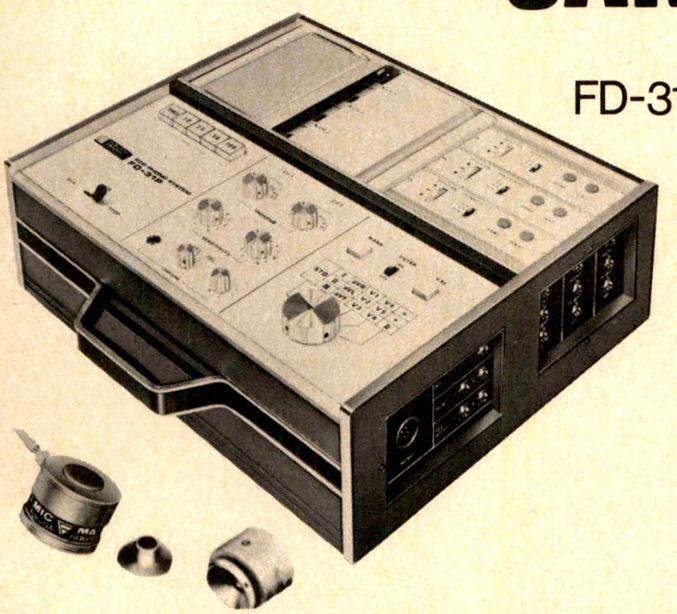

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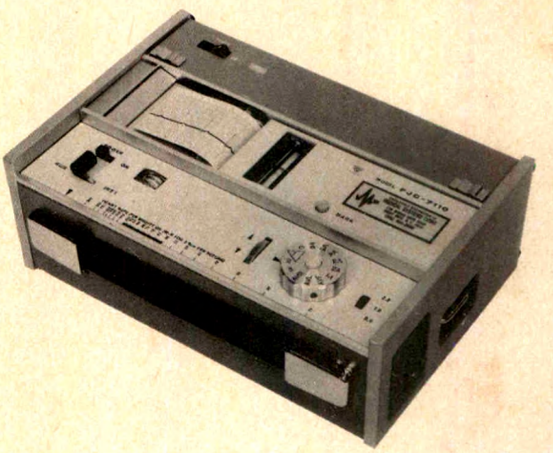

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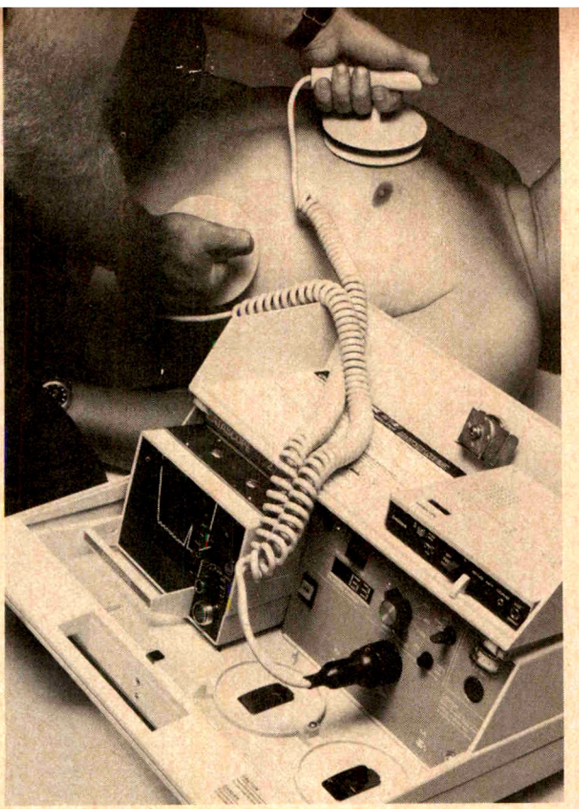

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Which means that in addition to offering more energy, our system offers more capability than any monitor/defibrillator in the world.

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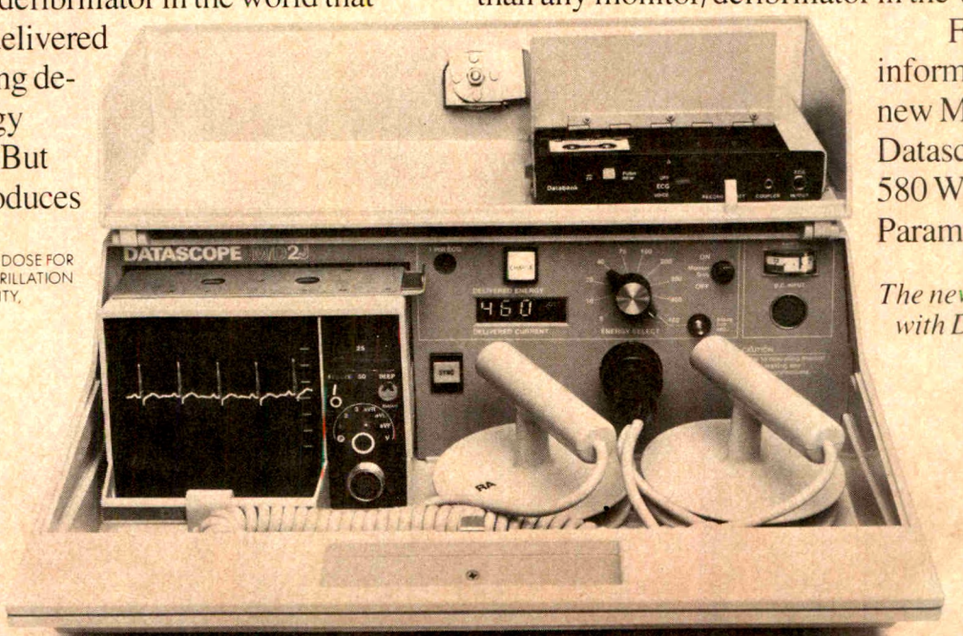
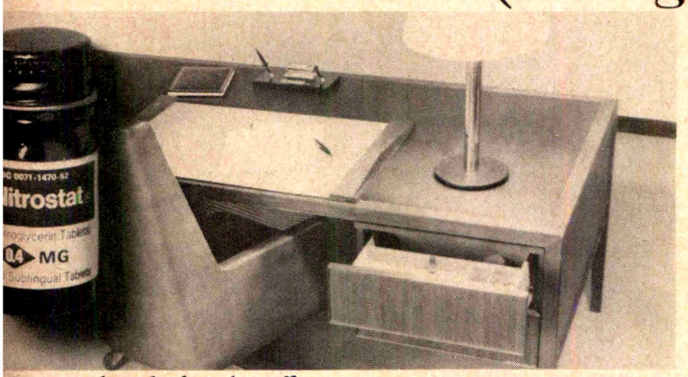


The new M/D2J with Databank.

TACKER, JR., W.A.: ELECTRICAL DOSE FOR EFIBRILLATION. CARDIAC DEFIBRILLATION ONFERENCE, PURDUE UNIVERSITY, GS. 121-7, OCT. '75.

The Datascope M/D2J.

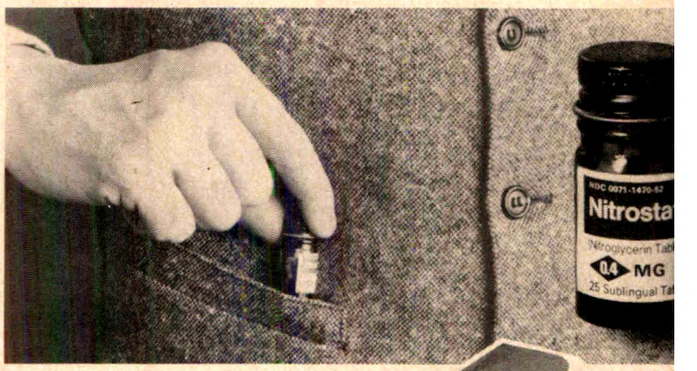
New convenience comes to nitroglycerin therapy: Nitrostat® 4x25s (nitroglycerin tablets, USP)



one bottle for the office

a second at home

a third for travel



and a fourth in pocket or purse

Nitrostat® 4x25s (nitroglycerin tablets, USP)

Sublingual Tablets—Stabilized Formula

- Stabilized sublingual nitroglycerin available *when* and *where* it is needed—four bottles of 25 tablets each

Minimize Change in Potency and Maximize Patient Convenience

- Replace patient's pillbox with Nitrostat 25s
- Four dosage strengths—0.15 mg (1/400 grain), 0.3 mg (1/200 grain), 0.4 mg (1/150 grain), 0.6 mg (1/100 grain)

(ACTUAL RETAIL PACKAGE SIZE)

Also available in single bottles of 100 tablets

PD-JA-1669-1-P (2-77)

PARKE, DAVIS & COMPANY
Detroit, MI 48232

PARKE-DAVIS

"How ARCO Medical Products Company is improving the predictability of cardiac pacing."

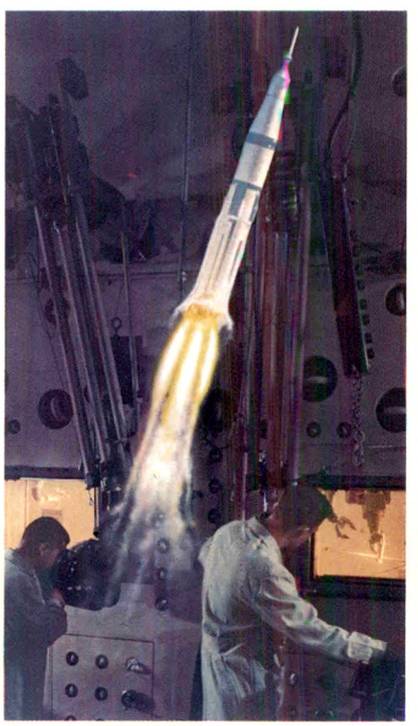
—an open letter to physicians and other members of the medical community from Page Thompson, President, ARCO Medical Products Company.

"ARCO Medical Products Company, a subsidiary of Atlantic Richfield Company—the 12th largest corporate entity in the United States, known principally for its chemical, petroleum and mineral operations—is now emerging as a leader in the highly specialized field of cardiac pacemaker systems. And we would like you to be sure that there are substantial benefits accruing to you and your patients due to our solid and rapidly growing position in this field.

"**To highlight a few of the benefits for you** we'd like to call your attention to the fact that ARCO Medical Products Company now provides:

- Pulse generators substantially improved in predictability
- A lithium thionyl chloride power source with highly desirable characteristics
- Significantly increased research and development to provide improved and new products in the near future
- A responsible attitude toward selling whereby we will not offer for sale what we cannot deliver—within 48 hours—anywhere in the free world
- Realistic, 'no-nonsense' product guarantees

"**To understand how it all began** look back to the early 1960s. Our people were then encapsulating nuclear materials used in the naval nuclear submarine program and the Apollo space program. As a result of this experience, we were awarded the first AEC contract for the encapsulation of nuclear material to be implanted in the



human body. That was the beginning of the first nuclear-powered pulse generator.

"The precision and expertise put into the manufacture of those first nuclear-powered units is apparent when you see they have been functioning effectively for ten years, with a long life expectancy still ahead of them.

"**The nuclear experience evolved** into the development of pacemaker technology that utilized the nuclear-precise production and quality assurance techniques perfected when working on the AEC contract.

"ARCO Medical Products Company helped develop the advanced and exclusive lithium thionyl chloride power cell, which does not build up internal pressure. ARCO Medical

Products Company developed the triple encapsulation process which virtually solved the problem of invasion and migration of moisture within the generators.
ARCO Medical Products Company developed both a component and a total unit 'burn-in' process which virtually eliminates initial failures.
In these ways, and in many others, ARCO Medical Products Company has succeeded in significantly improving the predictability of the pulse generator.

"**We are a concerned company,** and this concern has led us to a commitment that no other pulse generator company matches: improved pulse generators

supported by a 'no-nonsense' product guarantee. In essence:

1. In the event an ARCOlith™ pulse generator becomes defective for any reason up to and including 60 days following implant, ARCO Medical Products Company will furnish a replacement pulse generator at no charge and pay *all* surgical and hospital costs as established by third-party insurance company pay schedules.*
2. In the event an ARCOlith pulse generator becomes defective for any reason after 60 days following implant up to the end of the warranty period,* ARCO Medical Products Company will furnish a replacement pulse generator at no charge and pay up to a total of $200 for surgical and hospital costs over third-party insurance company pay schedules.*

"**Be involved.** Take a stand by communicating your thoughts to us. Whatever your concerns may be regarding our products, our business philosophy, or your hopes for the future of pacemaker technology, we would like to hear from you. Kindly use the form on the following page to jot down your thoughts and mail them to me. It will be a pleasure to share your ideas."

Page Thompson

*Refer to warranty for complete details.

ARCOlith™ 12, 6, and 4 are now the trade names for pulse generator models LI-2, LI-4 and LI-3.

We'd like to hear from you.

ARCO Medical Products Company invites you to communicate your thoughts regarding implantable pulse generators or manufacturer-physician relationships.

Get involved. Take a stand. Tell us what's on your mind so we can be of better service to you and your patients in the future:

Page Thompson, President
ARCO/Medical Products Company
Subsidiary of AtlanticRichfieldCompany
1500 Market Street
Philadelphia, PA 19101

Subject: _____

Name _____

Address _____

City _____

State _____ Zip _____

ARCO/Medical Products Company
Subsidiary of AtlanticRichfieldCompany

Improving the predictability of cardiac pacing

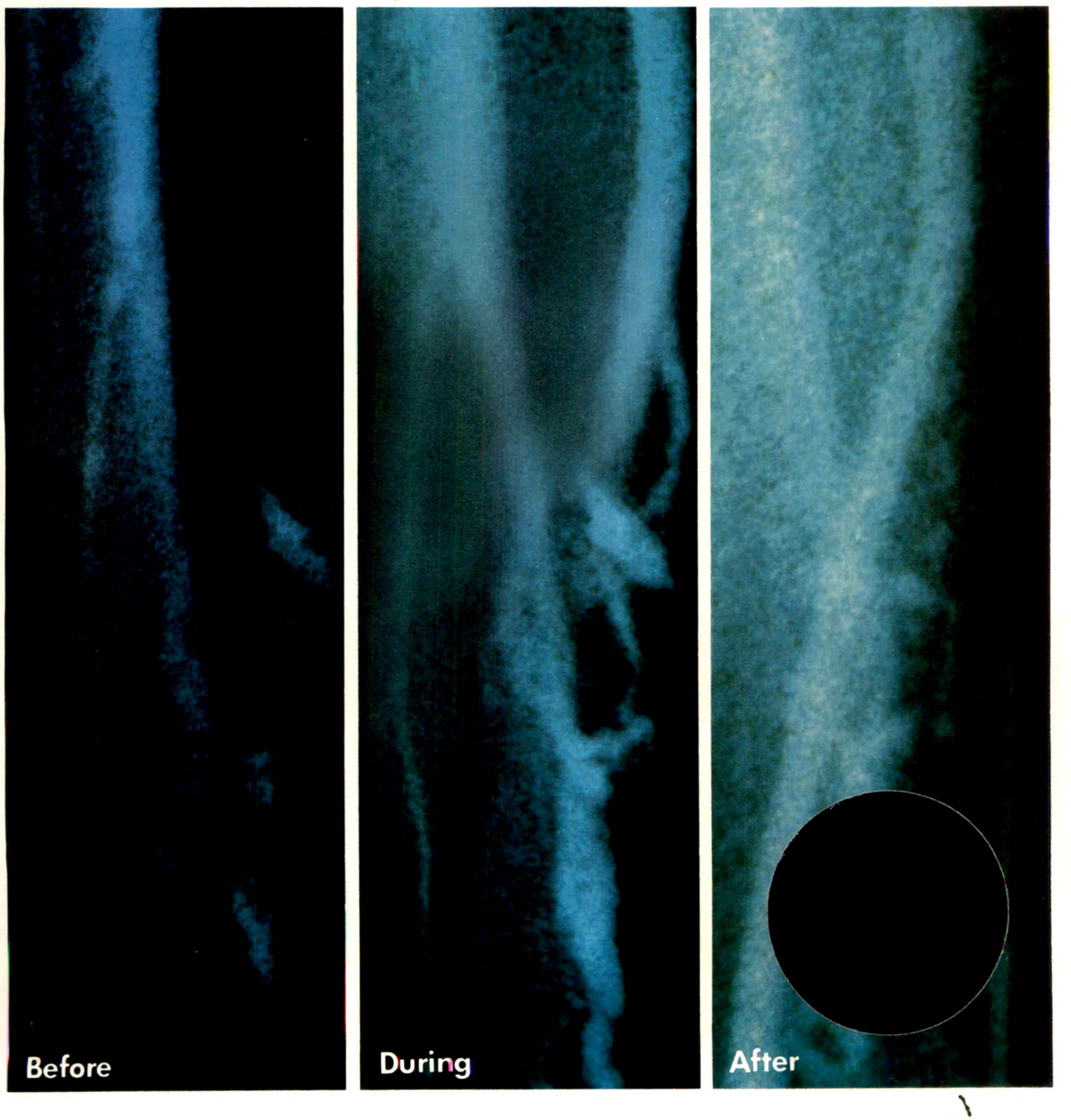
Corporate Headquarters
1500 Market Street
Philadelphia, PA 19101
(215) 557-2000

Technical Center
101 Sherman Avenue
Vandergrift, PA 15690
(412) 568-3663

Operations
P. O. Box 546
Leechburg, PA 15656
(412) 845-8111

You are looking at the dissolution of a thrombus.

Time required: 72 hours or less.



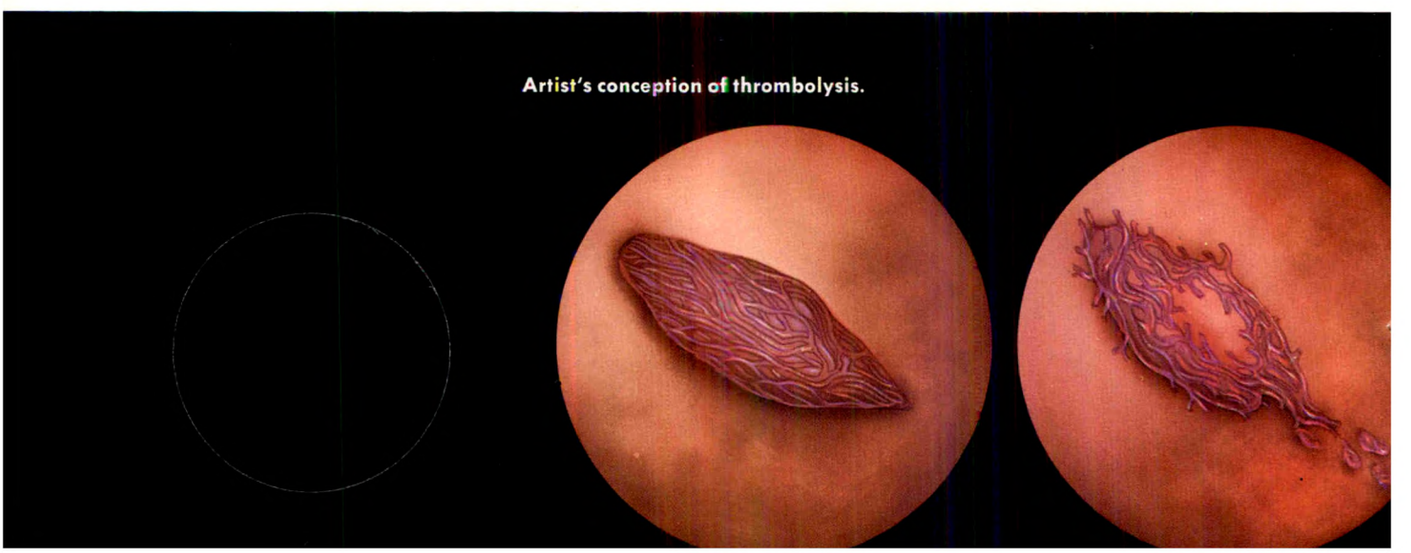
Introducing the first thrombolytic agent
for objectively diagnosed deep venous thrombi
and acute massive pulmonary emboli.

Hoechst-Roussel Pharmaceuticals Inc.

Announces
Streptase®
(streptokinase) I.V.

Now... a new alternative to surgery...

- **avoids the risks associated with thrombectomy.**
- **reduces the need for high-risk pulmonary embolectomy.**



To lyse venous thrombi and pulmonary emboli—intravenous Streptase®(streptokinase). Anticoagulant therapy is given following Streptase to prevent rethrombosis.

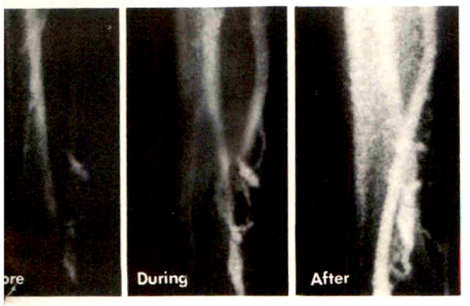
Now physicians have available a medical therapy for the early clearance of deep venous thrombi that is preferable to thrombectomy because it may preserve valvular function and avoid chronic stasis, although long-term benefits have not been established. And acute massive pulmonary emboli may be cleared without high-risk embolectomy.

A unique mode of action

New Streptase is the highly purified form of streptokinase, a bacterial protein derived from β-hemolytic streptococci. It combines with plasminogen to form an activator complex that converts residual plasminogen into the proteolytic enzyme plasmin. Plasmin hydrolyzes fibrin into polypeptides.

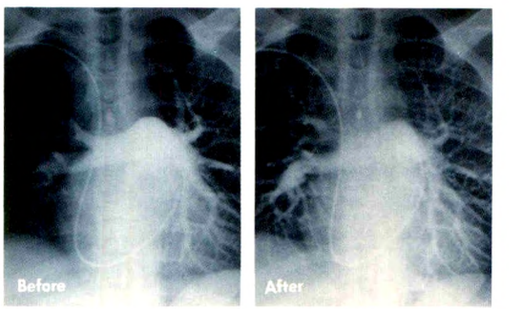
High rate of clinical success demonstrated by angiography:

In patients with venous thrombosis



In comparative controlled studies of 78 patients with venous thrombosis, Streptase produced complete or significant clearing of the thrombosis in 54% of patients while only 7% on conventional heparin therapy showed similar results.

In patients with pulmonary embolism



In studies of 124 patients with pulmonary embolism, complete or significant clearing was seen in 66% of the patients on Streptase but in only 11% of the heparin-treated patients.

Table I
Comparative angiographic results during controlled investigations*

Results	Venous Thrombosis		Pulmonary Embolism	
	Streptase (37 patients)	Heparin (41 patients)	Streptase (36 patients)	Heparin (88 patients)
Complete clearing	22%	5%	22%	5%
Significant, but incomplete, clearing	32%	2%	44%	6%
Minimal clearing	21%	20%	20%	43%
No change	22%	66%	14%	35%
Worse	3%	7%	0%	11%

In most cases, clearance was achieved in 72 hours or less.

For best results, Streptase should be used within 2 weeks after onset of venous thrombosis symptoms and within 5 days after onset of pulmonary embolism symptoms. Please see last page of this advertisement for a brief summary of prescribing information.

*Data on file and available on request from Hoechst-Roussel Pharmaceuticals Incorporated. Pulmonary embolism data include those taken from National Heart and Lung Institute study.

Thrombosis and thrombolysis information available

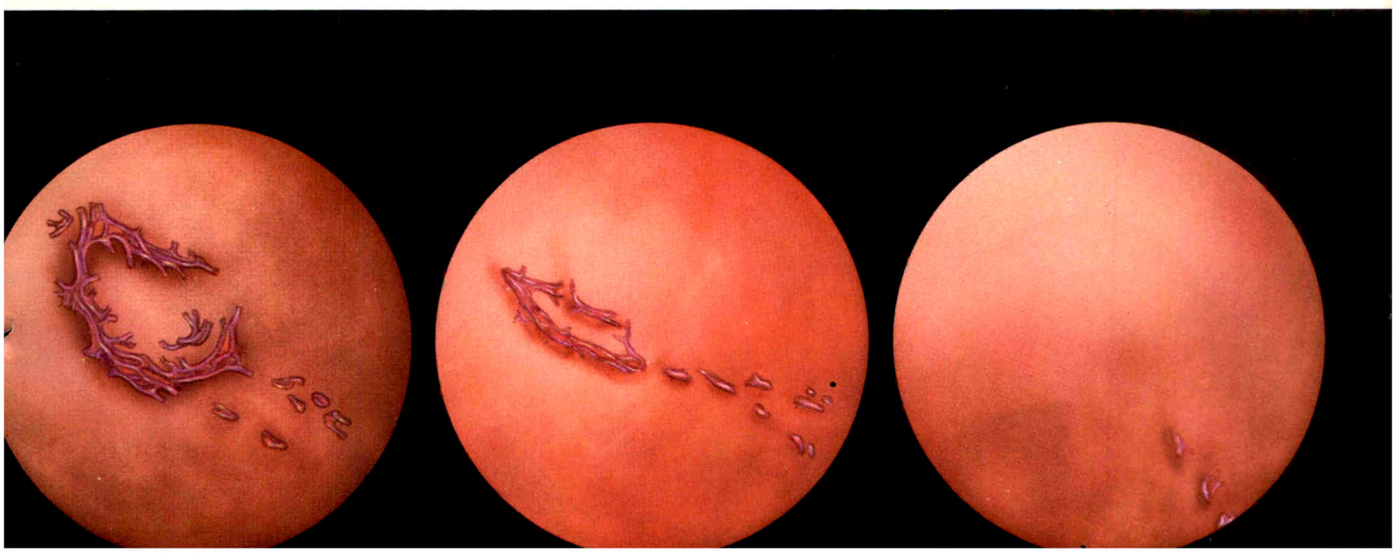
When considering the use of Streptase (streptokinase), comprehensive knowledge of prescribing information and strict observance of the contraindications, warnings, precautions, and dosage and administration instructions are most important to minimize the incidence and severity of adverse reactions, the most significant and frequent being fever, allergy and bleeding. Use of Streptase requires an interdisciplinary effort and therefore should be reserved for those hospitals with facilities for angiography, coagulation testing and volumetric or syringe pump administration of Streptase intravenously.

Hoechst-Roussel has prepared a comprehensive educational program on thrombosis and thrombolysis that includes two films, associated monographs, dosage and administration guidelines and a Speakers Bureau of physicians experienced in the use of thrombolytic therapy.

For information, interested physicians may contact Scientific Services, Room 236, Building M, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876, (201) 685-2611, or the local Hoechst-Roussel Sales Representative.

For a complete list of indications, contraindications, warnings, precautions, adverse reactions and dosage information, please refer to the full prescribing information for Streptase, a summary of which appears on the following page.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876



Streptase®
(streptokinase) I.V.

Brief Summary of the Prescribing Information

Streptase® (streptokinase) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring can be performed. The full prescribing information should be read for complete details.

When considering treatment with Streptase® (streptokinase) the overall clinical status and history of the patient should be carefully assessed. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with Streptase® (streptokinase) therapy than with heparin or oral coumarin compound anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient should be weighed against the potential benefits of treating the patient with Streptase® (streptokinase).

Indications

Pulmonary Embolism: Streptase® (streptokinase) is indicated in adults for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels. It may also be indicated for embolization accompanied by unstable hemodynamics. The diagnosis should be confirmed by objective means. Streptase® (streptokinase) treatment should be instituted as soon as possible after onset of symptoms and no later than five days after onset. Reduction of morbidity or mortality has not been established.

Deep Vein Thrombosis: Streptase® (streptokinase) is indicated for lysis of acute, extensive thrombi of the deep veins in adults. Diagnosis should be confirmed by objective methods.

Streptase® (streptokinase) should be administered as soon as possible after the onset of the thrombotic event (preferably within several days), although slight enhancement of clot lysis has been shown with initiation of therapy up to two weeks after the onset of symptoms.

Contraindications

Predisposition to Bleeding: Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated when the following conditions exist: surgery within 10 days, liver or kidney biopsy within 10 days, intraarterial diagnostic procedure within 10 days, ulcerative wound, recent trauma, visceral carcinoma, parturition (within 10 days), ulcerative colitis or diverticulitis, hypertension, liver or kidney disease, thrombocytopenia or other evidence of defective hemostasis, active tuberculosis, subacute bacterial endocarditis, gastrointestinal bleeding within 6 months.

Predisposition to Allergy: Streptase® (streptokinase) is contraindicated in patients with a history of a previous severe allergic reaction to Streptase® (streptokinase) or who present a significant risk of an allergic response.

Recent Cerebral Embolism, Thrombosis, or Hemorrhage: Treatment with Streptase® (streptokinase) is contraindicated for at least two months.

Predisposition to Systemic Infection: Use of Streptase® (streptokinase) in septic thrombophlebitis may be hazardous because of the risk of inducing systemic infection.

Warnings

Bleeding: Activation of the fibrinolytic system with Streptase® (streptokinase) results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy. Although the aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for lysis of intravascular deposits of fibrin, other fibrin deposits are also destined for lysis and bleeding may result. The possibility of bruising or hematoma formation especially with intramuscular injections is high.

Bleeding at sites of recent invasive procedures may occur. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. Also, invasive venous procedures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observations.

Spontaneous bleeding from internal sites may also occur.

Should serious spontaneous bleeding occur, the infusion of Streptase® (streptokinase) should be terminated immediately.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. These products possess an anticoagulant effect and should be monitored by serial thrombin time determinations.

Predisposition to Cerebral Embolism: Treatment with Streptase® (streptokinase) of patients with conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Allergy: Streptase® (streptokinase) is antigenic, thus, allergic reactions including anaphylaxis may occur.

Recipients of Streptase® (streptokinase) should be observed carefully during the first few hours of therapy. Patients with known allergies to other antigens are more likely to react. If significant changes in blood pressure or asthmatic symptoms occur which might be due to allergy, the infusion should be terminated and symptomatic treatment employed.

Other mild allergic manifestations have also been observed but generally are not serious enough to require discontinuation of therapy.

Use of Anticoagulants: Concurrent use of anticoagulants with Streptase® (streptokinase) is not recommended and may be hazardous. A thrombin time of less than twice the normal control value is adequate for starting Streptase® (streptokinase) infusions safely following the use of heparin. Heparin should not be started following Streptase® (streptokinase) therapy until the thrombin time has returned to less than twice the normal control value.

In order to minimize rethrombosis, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following Streptase® (streptokinase) therapy.

Use in Pregnancy and in Children: Streptase® (streptokinase) therapy during pregnancy and in children is not recommended.

Precautions

If the patient's history gives rise to suspicion of elevated resistance, the streptokinase resistance test should be used to determine the proper loading dose. When resistance levels in excess of 1,000,000 I.U. are found, Streptase® (streptokinase) should not be administered.

Streptase® (streptokinase) infusions have been associated with altered platelet function. Concurrent use of drugs that may potentiate this effect should be avoided.

Adverse Reactions

Incidence and Management

Bleeding: Severe spontaneous bleeding has been documented in 6 of 292 patients during Streptase® (streptokinase) treatment. Several fatalities due to cerebral hemorrhage have occurred during Streptase® (streptokinase) therapy. Less severe spontaneous bleeding has been observed during Streptase® (streptokinase) treatment at approximately twice the frequency as that occurring during heparin therapy. In several instances, spontaneous bleeding has been traced to concomitant anticoagulant treatment which is not recommended.

Management of Severe Bleeding: Streptase® (streptokinase) therapy must be discontinued. If very rapid reversal of the fibrinolytic state is required, treatment with aminocaproic acid (EACA) can be instituted.

Plasma volume expanders are indicated to replace blood volume deficit. If blood loss has been large, Red Blood Cells (Human) may also be indicated. If only Whole Blood (Human) is available, it may also be used.

Allergic Reaction

Incidence: Reactions determined to represent possible anaphylaxis have been observed in 7 of 292 patients treated with Streptase® (streptokinase). These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling, or angioneurotic edema. Other milder allergic effects have been observed in approximately 12% of patients. There was no apparent relationship to dosage.

Management of Allergic Reactions: Mild and moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with corticosteroids administered intravenously as required.

Fever

Incidence: One-third of patients treated with Streptase® (streptokinase) have shown increases in body temperature of 1.5°F or more; the incidence of fever ≥104°F was 3.4%.

Management: Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommenced.

Phlebitis: Phlebitis near the site of intravenous infusion of Streptase® (streptokinase) has occurred in less than 2% of patients.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 ml vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows: 100,000 IU (yellow), 250,000 IU (green), 750,000 IU (blue).

In each vial there is a 20% overfill above that stated on the label. Each vial also contains 25 mg cross-linked gelatin polypeptides and 25 mg sodium L-glutamate as stabilizers.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876
REG TM HOECHST AG

Distributed by
Hoechst-Roussel Pharmaceuticals Incorporated
Manufactured by Behringwerke AG
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CARDIO-BIONIC-SCANNING INC.

SCANNING DATA SHEET

PATIENT _____ DATE 10/10/77 - 10/11/77

ADDRESS _____ SEX _____ AGE _____

HOSPITAL Hospital I.D. # _____

PHYSICIAN _____

QUALITY OF RECORDING	PATIENT DIARY SUBMITTED	SYMPTOMS REPORTED	CALIBRATIONS
[X] GOOD [ ] FAIR [ ] POOR	[X] YES [ ] NO	[X] YES [ ] NO	[X] YES [ ] NO

HOUR	VENTRICULAR * ECTOPIC BEATS	PVC's * PER 1000 BEATS	SUPRAVENTRICULAR ECTOPIC BEATS	ST-T CHANGES IN MM	TOTAL BEATS	RATE
4-5pm	5	3	0	-0.5		62
5-6	7	4	21	0		68
6-7	16	7	10	-1.0	total	66
7-8	12	5	1	-0.5	beats:	68
8-9	24	10	5	0	87088	62
9-10	18	8	2	0		65
10-11	30	11	3	0		61
11-12	15	7	3	**		58
12-1 am	35	13	4	**		50
1-2	61	20	0	0		57
2-3	20	9	2	-0.5		59
3-4	19	8	4	+1,0		51
4-5	11	5	2	+1.5		49
5-6	3	10	5	**		52
6-7	40	16	1	-1.0		57
7-8	19	8	1	-1.0		70
8-9	19	28	0	-0.5		77
9-10	68	29	5	-1.0		69
10-11	25	10	1	-0.5		68
11-12	18	8	1	-1.0		64
12-1 pm	7	4	0	-0.5		74
1-2	13	6	3	-0.5		66
2-3	2	2	12	-0.5		70

HEART RATE

MAXIMUM OF *159 BEATS PER MINUTE AT 12:24am MINIMUM OF **30 BEATS PER MINUTE AT 11:53am

*starts & ends abruptly, 3.8 sec. longest R-R interval @ 4:12pm, 3.04 sec.

**see writeouts.

Peter L. Bond, M.D.

THIS IS NOT A PHYSICIAN'S INTERPETATION – ONLY SUPPLEMENTAL INFORMATION TO THE DATA SCANNING STRIPS.

* (Premature Ventricular Contractions (PVC's) and Premature Supraventricular Contractions with Aberrant IV Conduction)

ml

No other scanning service gives you this report.

Clarity! Brevity! Precision!

These are the qualities every scanning service should offer to save you time and trouble.

But only CBS is equipped to offer ...a lot more important extras – like:

The only total scan system designed by a Cardiologist;

The latest Holter monitors customized by us for improved performance;

Up to 60% more vital information with the most complete report in the industry;

Four monitoring programs available with no capital investment.

To know more about why CBS is the only total scan and supply service clip the coupon and mail it today. If you believe in the importance of Holter monitoring then you owe it to yourself and your patients to look into Cardio-Bionic-Scanning.

CARDIO-BIONIC SCANNING INC.

200 East Eckerson Rd., Spring Valley, N.Y. 10977
(914) 425-1838, Or call toll free (800) 431-1882

AJC-28

Cardio-Bionic-Scanning Inc.
200 East Eckerson Road
Spring Valley, New York 10977

Please send me more information about the Cardio-Bionic-Scanning service.

Name, Title

Organization

Address

State Zip Phone

See us at the American College of Cardiology Meeting, Anaheim, CA (March 6-9).

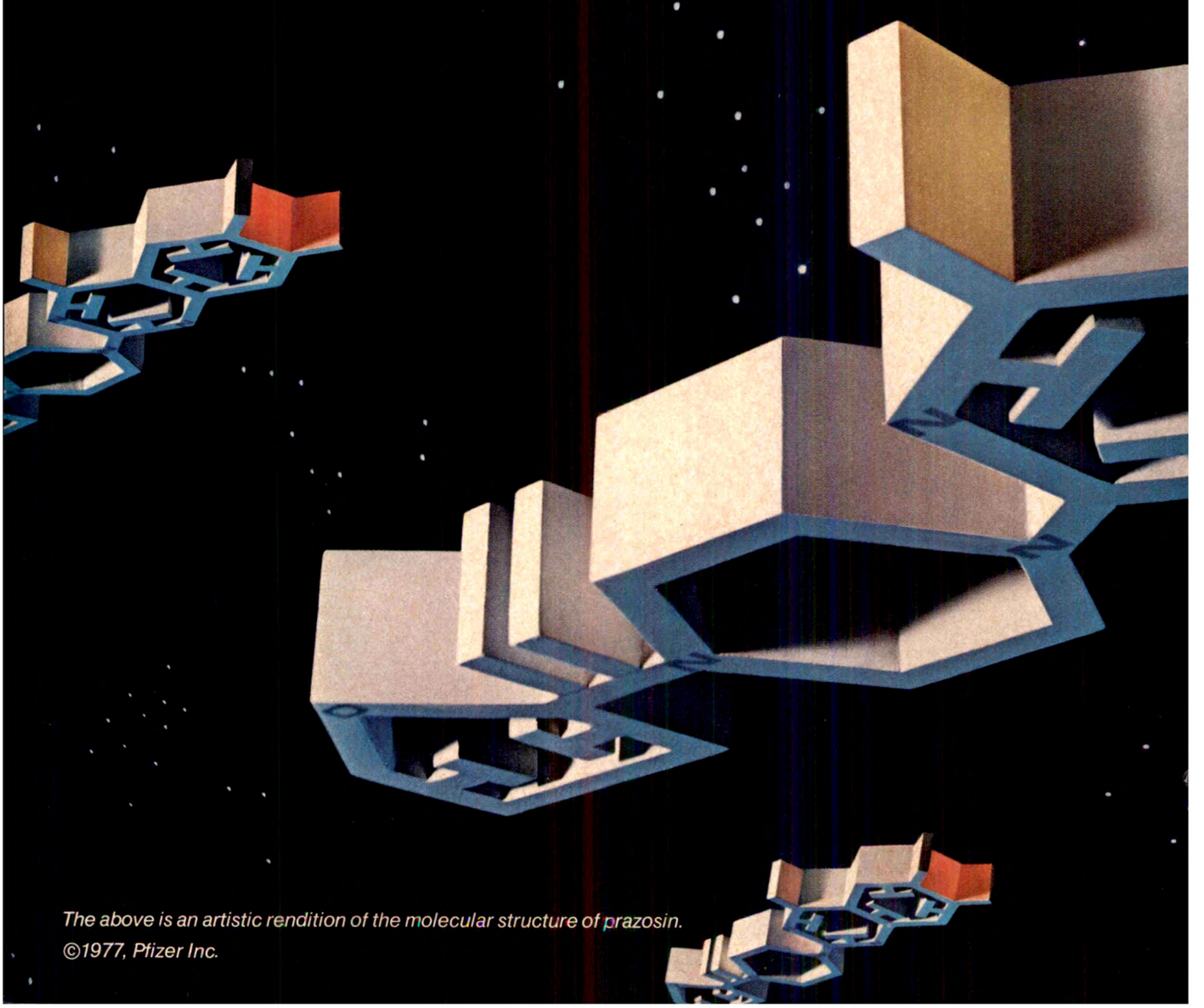
A89

FROM PFIZER...

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

A FLEXIBLE ANTIHYPERTENSIVE— ALONE OR IN COMBINATION

- chemically and pharmacologically unique vasodilator
- mild to moderate in activity
- effective in all grades of hypertension
- well suited for long-term therapy*
- no tolerance observed in long-term therapy*



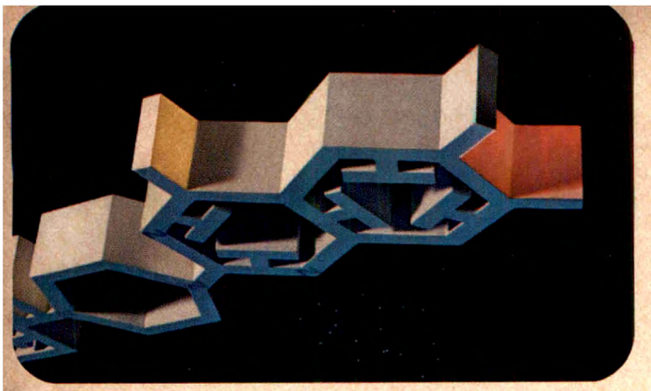
The above is an artistic rendition of the molecular structure of prazosin.

©1977, Pfizer Inc.

*Minipress has been studied in patients on continuous therapy for periods of up to 5 years.

Before prescribing Minipress, WARNINGS and DOSAGE AND ADMINISTRATION sections should be carefully reviewed.

Please see Brief Summary on last page for indications, warnings and adverse reactions.



WELL SUITED FOR LONG-TERM THERAPY...

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

- Chemically and pharmacologically unique vasodilator.
- Mild to moderate in activity.
- Effective in all grades of hypertension, either alone or in combination with a diuretic and/or other antihypertensive agent.
- Direct action on the arterioles without clinically significant effects on cardiac output, renal blood flow or glomerular filtration rate. Reflex tachycardia frequently associated with other vasodilators is much less common with Minipress.
- No tolerance observed in long-term therapy in patients on continuous therapy for periods of up to 5 years.
- Studies in patients on continuous therapy for periods of up to 5 years indicate that Minipress is well suited for long-term therapy.
- Side effects most frequently experienced with Minipress in a series of 934 patients were: dizziness (10.3%), headache (7.8%), drowsiness (7.6%), lack of energy (6.9%), weakness (6.5%), palpitations (5.3%), and nausea (4.9%). A small percentage of patients have experienced orthostatic hypotension (3.4%) and syncope (1.3%). (For a more detailed description of orthostatic hypotension and syncope, see Warnings in Brief Summary before initiating therapy with Minipress.)
- Starting dosage: 1 mg t.i.d.
- Usual maximum recommended dosage: 20 mg daily, given in divided doses.
- Some patients can be maintained adequately on a b.i.d. dosage regimen.
- Available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit dose packages of 100 (10 x 10's).

More detailed information available on request.

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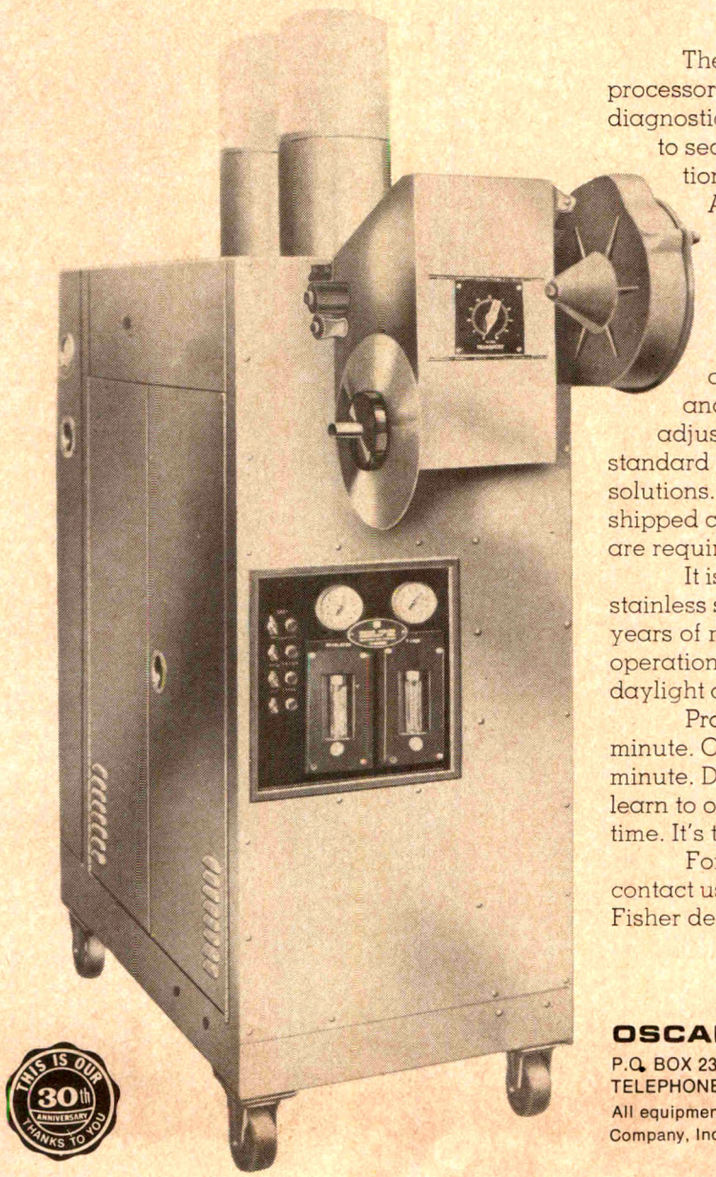

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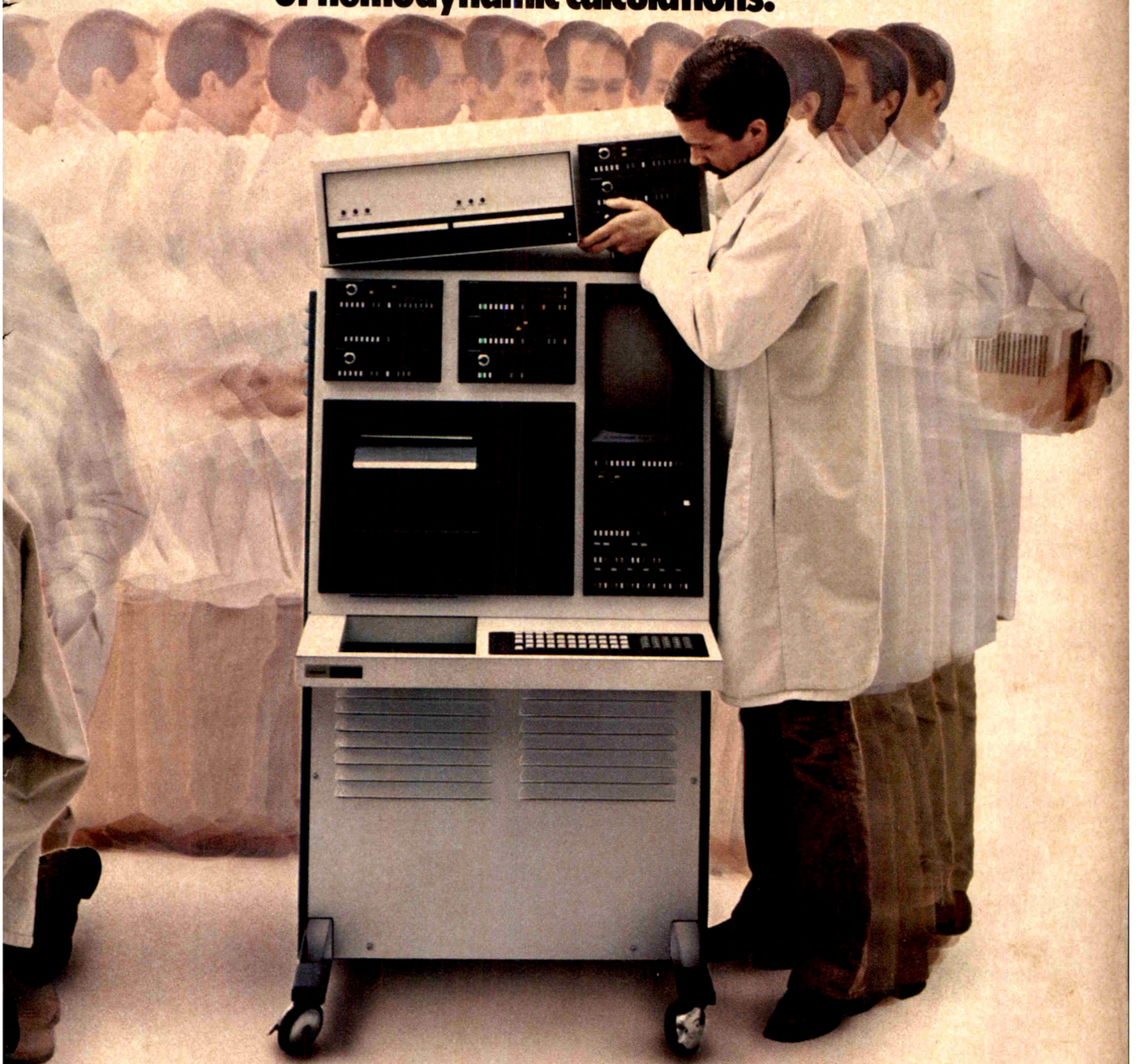

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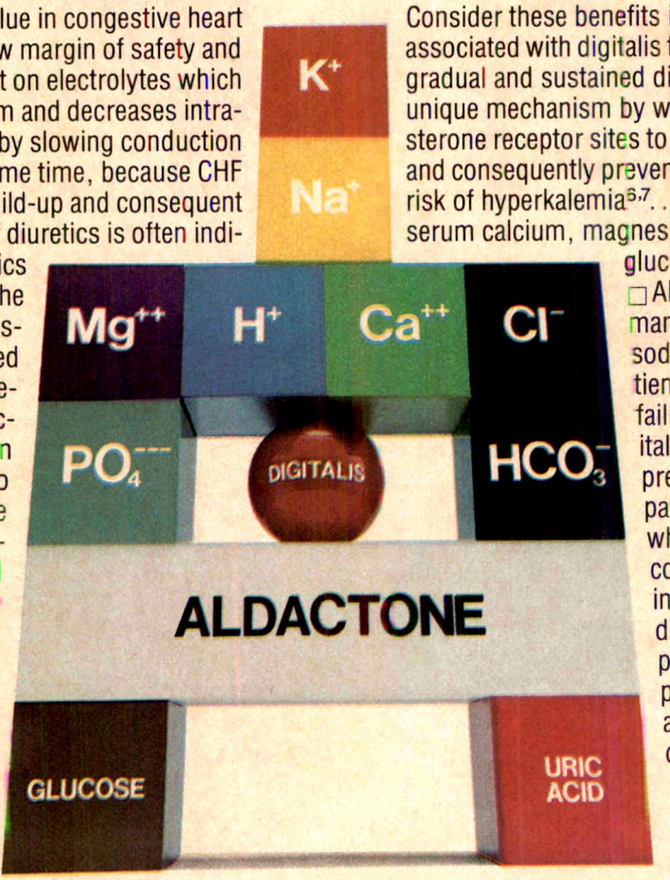
Unfortunately, electrolyte imbalance is often a problem during digitalis therapy. And most diuretics worsen the problem.

Despite its therapeutic value in congestive heart failure, digitalis has a narrow margin of safety and toxic levels produce an effect on electrolytes which increases intracellular sodium and decreases intracellular potassium, thereby slowing conduction in cardiac tissues. At the same time, because CHF encourages sodium build-up and consequent edema, concomitant use of diuretics is often indicated. □ Use of most diuretics can increase problems for the patient on digitalis, and excessive loss of potassium caused by potent diuretics is a frequent cause of digitalis toxicity.[1,2] Potassium depletion sensitizes the myocardium to digitalis and can set the stage for serious cardiac arrhythmias even with normal dosage.[3] □ Clearly, any diuretic choice should be carefully analyzed for its effect on electrolyte balance. Thiazides, for example, can induce hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.[4] They can also decrease uric acid excretion and impair glucose tolerance. In treatment with furosemide, too, fluid and electrolyte imbalance is the most common form of clinical toxicity.[5]



Fortunately, concomitant diuretic therapy with Aldactone® (spironolactone) can help maintain the delicate electrolyte balance . . . when other measures won't do.

Consider these benefits in avoiding the problems associated with digitalis therapy: Aldactone provides gradual and sustained diuresis . . . works through a unique mechanism by which it competes for aldosterone receptor sites to normalize body potassium, and consequently prevents hypokalemia with limited risk of hyperkalemia[6,7] . . . does not adversely affect serum calcium, magnesium and uric acid levels or glucose tolerance.[7]

□ Aldactone is indicated for management of edema and sodium retention in those patients with congestive heart failure who are taking digitalis, or in the treatment or prevention of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate. □ When diuretic therapy is indicated, prescribe Aldactone to help preserve the delicate balance of electrolytes during digitalis therapy.

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3. Cardiac Glycosides, Section 4, in Kastrup, E. K. (Editor): Facts and Comparisons, St. Louis, Facts and Comparisons, Inc., Jan. 1975, pp. 140-141C.
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6. Laragh, J. H.: Diuretics in the Management of Congestive Heart Failure, Hosp. Pract. *5*:43-50 (Nov.) 1970.
7. Tobian, L. J., Jr.: The Clinical Approach to Essential Hypertension, Hosp. Pract. *10*:33-44 (July) 1975.

SEARLE

Aldactone®

(spironolactone) 25 mg. tablets

Before prescribing, please consult the complete prescribing information, a brief summary of which follows.

ALDACTONE®
(spironolactone) 25 mg. tablets

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./ kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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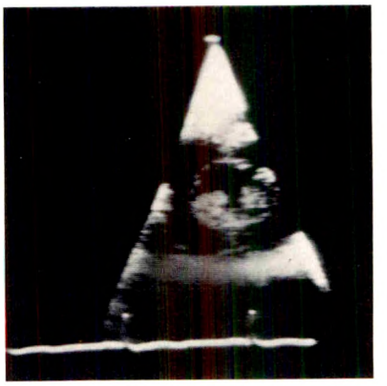
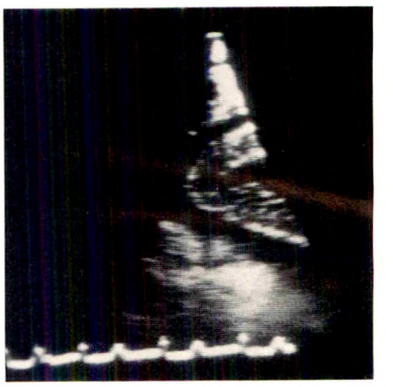


Transverse view of Left Ventricle, Papillary Muscle.



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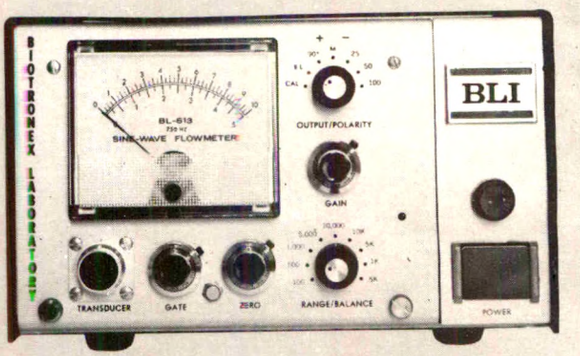

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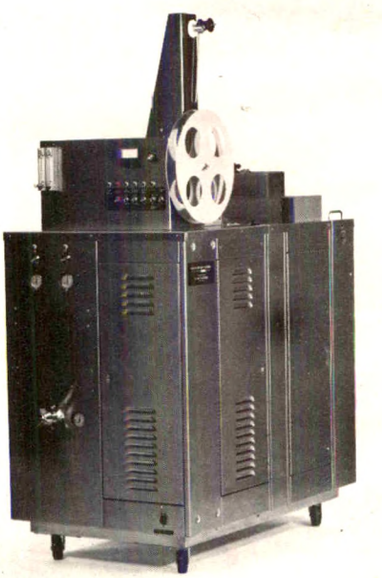

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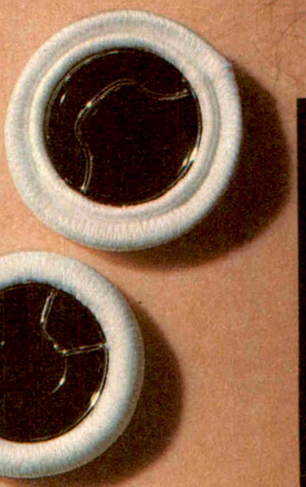

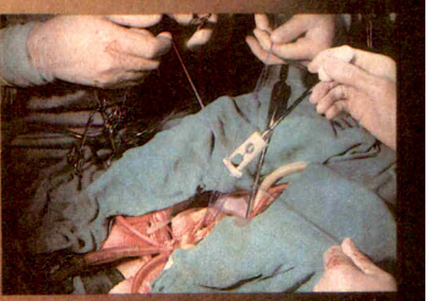

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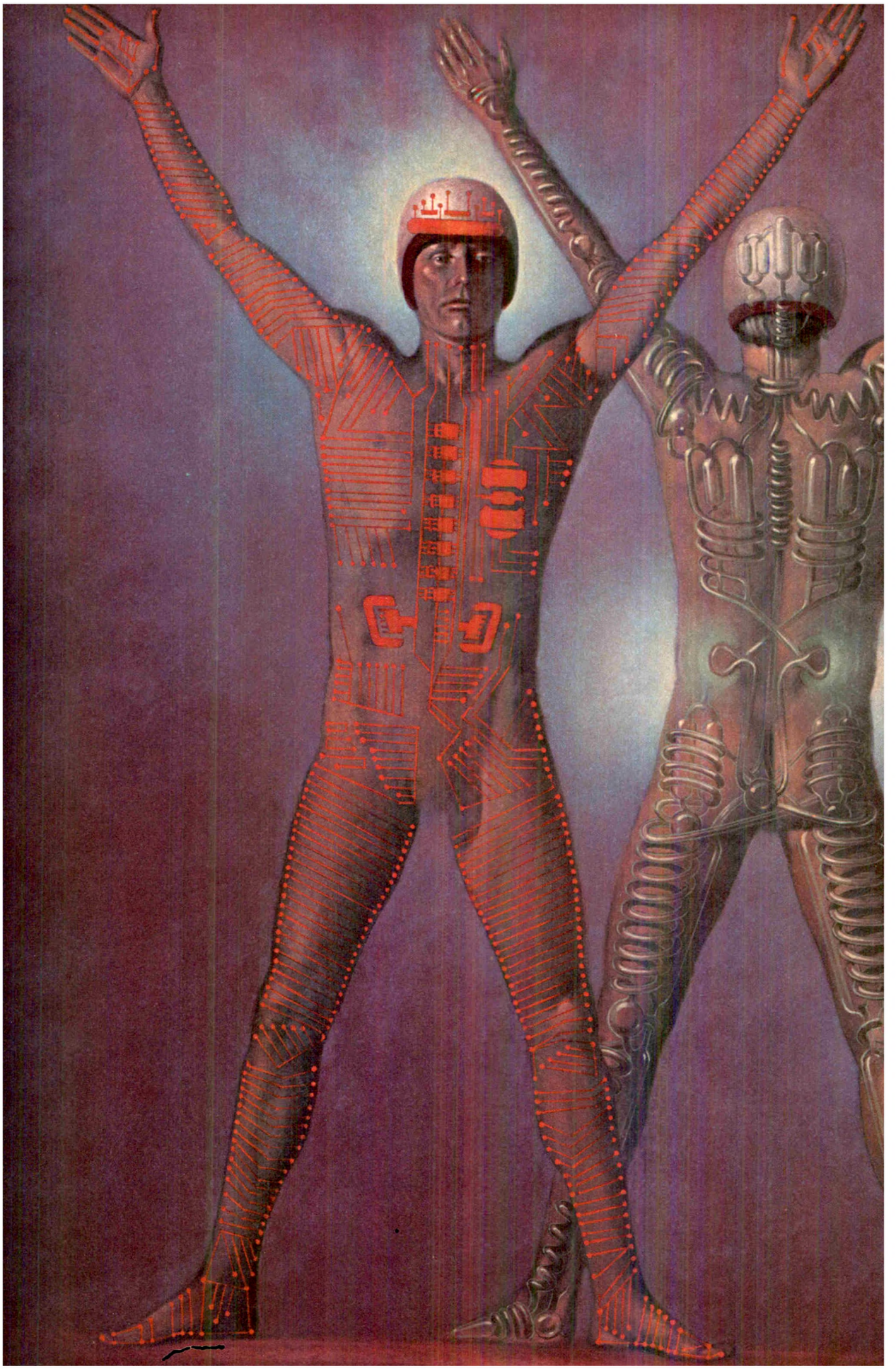

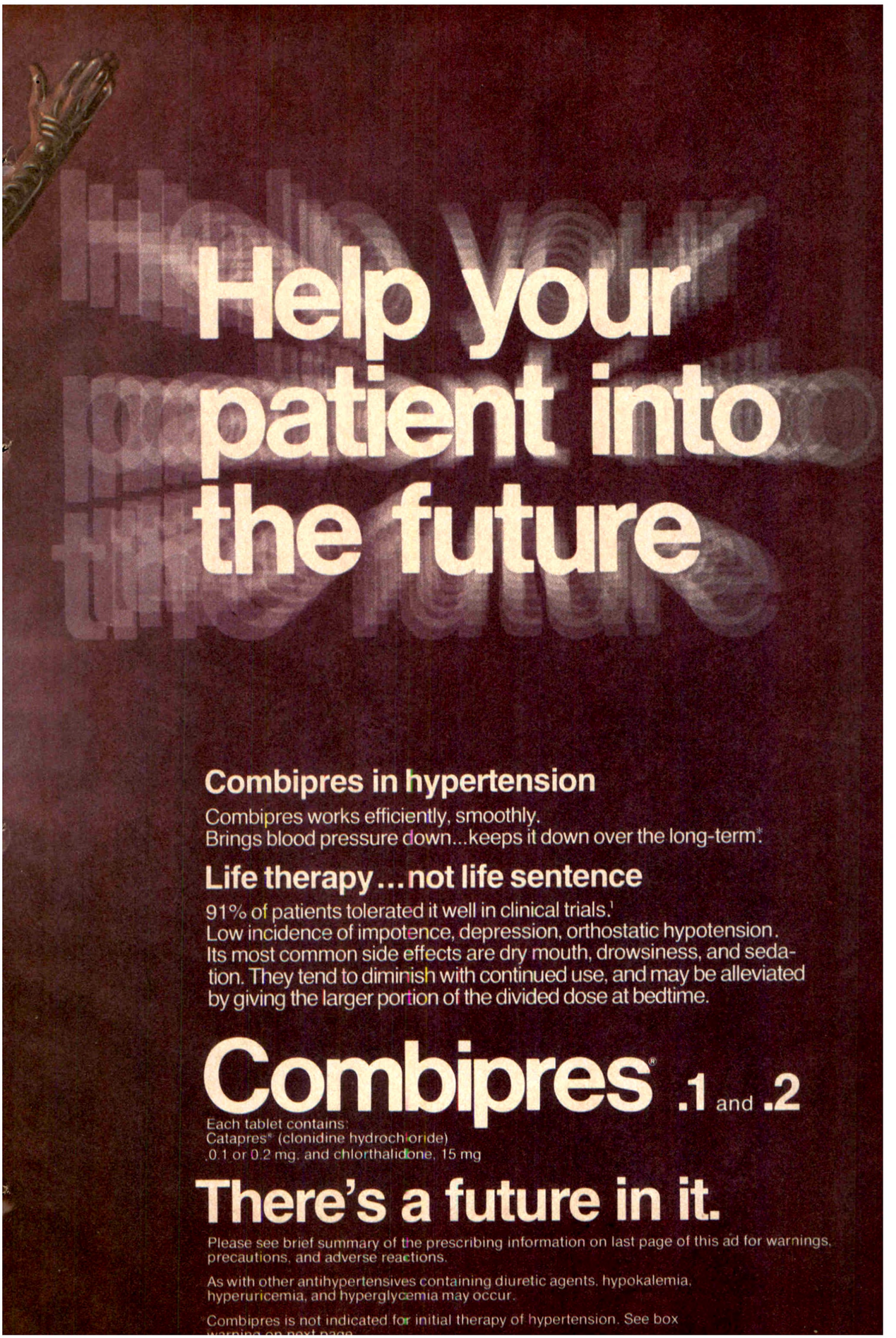
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Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

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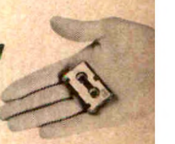

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The Myocardial Supply:Demand Ratio—A Critical Review

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Myocardial ischemia occurs when there is an imbalance between myocardial oxygen demand and supply, and it is usually entirely or predominantly subendocardial. Animal experiments have shown that relative subendocardial ischemia (a reduced inner:outer flow ratio) can be predicted quite accurately from the ratio of two pressure-time areas: DPTI, the area between diastolic aortic and left ventricular pressures, and SPTI, the area beneath the systolic left ventricular pressure curve. Although the importance of relating supply and demand is obvious, care is needed in applying the results of these animal experiments to man. Recent work has shown that the critical DPTI:SPTI ratio below which subendocardial ischemia occurs is about 0.4 to 0.5 rather than 0.7 to 0.8, as originally reported. On the other hand, the critical ratio may be raised to an unknown extent by myocardial edema or hypertrophy, or by thickened or narrowed coronary arteries. Furthermore, the critical ratio is not independent of absolute coronary diastolic pressure: It is much lower than 0.4 when coronary pressures are high, perhaps because intramyocardial diastolic pressures are much higher than once thought. Further work is required to allow an important physiologic concept to be used in making decisions about patients with heart disease.

In 1972 we[1] described a pressure ratio (DPTI:TTI) that was regarded as the supply:demand ratio of the left ventricle and correlated well with the ratio of subendocardial to subepicardial blood flow in dogs. The numerator of the ratio, termed the diastolic pressure-time index (DPTI), is the area between the aortic and left ventricular pressures in diastole; its units are mm·Hg·sec per beat or mm·Hg·sec × heart rate per min. When subendocardial vessels are maximally dilated, as may occur with severe anemia or hypoxemia, increased cardiac work or decreased coronary blood flow, then the diastolic pressure-time index represents the average time and driving pressure available for perfusing the subendocardial muscle each beat or each minute. The denominator of the ratio is the tension-time index (TTI) of Sarnoff et al.[2] and is the area under the left ventricular pressure curve in systole: it has the same units as the diastolic pressure-time index. This systolic area bears a fairly good relation to left ventricular myocardial oxygen consumption. In experiments in open chest, anesthetized dogs, the DPTI:TTI ratio was changed in various ways.[1,3–5] As long as the DPTI:TTI ratio was over 0.7, left ventricular subendocardial flow per gram roughly equalled subepicardial flow per gram; the ratio of these two flows is often termed the endocardial:epicardial flow ratio or the inner:outer flow ratio, and is normally between 0.8 and 1.2. When DPTI:TTI was reduced below 0.7 there was a linear decrease of the inner:outer flow ratio as DPTI:TTI became lower.

The importance of a predictive ratio like DPTI:TTI is great and many investigators are beginning to apply it to man, both in health and disease. For example, sudden maximal exercise in healthy men has been shown

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to produce electrocardiographic evidence of ischemia and a low DPTI:TTI ratio.[6] In children with aortic stenosis there is an association between electrocardiographic signs of subendocardial ischemia or symptoms and a similar pressure ratio.[7,8] Adults with severe aortic stenosis who have clinical, chemical or electrocardiographic evidence of ischemia have a low DPTI:TTI ratio that can be further depressed with isoproterenol.[9] Diastolic flow and resistance in a coronary bypass graft are closely correlated with the DPTI:TTI ratio.[10] Patients with severe aortic incompetence and congestive heart failure have a reduced diastolic pressure time index[11]; other clinical conditions could be listed. Low DPTI:TTI ratios have been associated with subendocardial hemorrhage and necrosis in patients who died after open heart surgery,[12,13] and regulation of balloon counterpulsation by a similar ratio has been suggested.[13] All of these findings are potentially important for patients with heart disease. However, although the principles on which the ratio was based come from well known physiologic studies of the coronary circulation, we are concerned about the dangers that may occur if this ratio is applied to patients without recognition of its limitations and without an understanding of all the factors that have gone into the experimental work. We will therefore comment briefly on the meaning of each component of the ratio, on the critical value of the ratio and on possible misinterpretations of the inner:outer flow ratio in animal experiments in which the pressure ratio has been studied.

Diastolic Pressure Time Index (DPTI)

When the subendocardial vessels are maximally dilated, flow through them depends on driving pressure, time and blood viscosity; driving pressure is the difference between the pressure in the coronary arteries and the opposing pressure in the small coronary vessels. If we consider first animals or people with normal blood viscosity then by the conventional Ohm's law relation, the following equation applies:

> Flow = $(P_1\text{-}P_2)/R$ min, where flow is measured in ml·min^{-1}·g^{-1}, $(P_1\text{-}P_2)$ is the driving pressure across the coronary vascular bed in mm Hg, and R min is the minimal coronary vascular resistance at maximal vasodilatation (mm Hg·ml^{-1}·min·g).

If this minimal resistance per gram of left ventricle is relatively constant (and it appears to be so in dogs and man), then subendocardial flow at maximal vasodilatation is proportional to the reduction in pressure across the coronary vascular bed. Because subendocardial flow is intermittent, occurring only in diastole, subendocardial flow is proportional to the average reduction in pressure multiplied by the duration of diastole; that is, it is proportional to the diastolic pressure-time index. This proportionality is true only if the vessels are maximally vasodilated. If they are not, then autoregulatory change in vascular resistance will keep subendocardial flow constant when the diastolic pressure-time index changes.[14]

Intramyocardial pressure in diastole versus coronary diastolic pressure: Calculation of the diastolic pressure-time index from pressure tracings is easy, but there is uncertainty about what the actual opposing pressure is. We have used the left ventricular diastolic pressure because it is similar to the intramyocardial pressure in diastole, but there have been no good studies of this relation.[5] If coronary sinus or right atrial pressure exceeds left ventricular diastolic pressure then this higher pressure represents the pressure opposing left ventricular coronary flow and so should be used to calculate the diastolic pressure time index. Even that, however, may not be correct. If subendocardial vessels are squeezed closed by high intramyocardial pressures in systole, then some finite pressure and time will be required to reopen them in diastole. Furthermore, intramyocardial tissue pressures in diastole may be much higher than previously believed. Studies by Archie,[15] confirmed by some of ours,[14] suggest that diastolic subendocardial tissue (closing) pressure is about 20 mm Hg or more, so that perhaps the opposing pressure used to calculate the diastolic pressure-time index is higher than we now use. The effect of this is to make the diastolic pressure-time index as we calculate it too high. For example, if the duration of diastole is 0.4 second, mean coronary diastolic pressure is 45 mm Hg and mean left ventricular diastolic pressure is 5 mm Hg, then the diastolic pressure-time index will be calculated as 0.4(45 − 5) or 16 mm Hg·sec. If the mean subendocardial tissue pressure is actually 25 mm Hg, then the true pressure head for perfusion will be 0.4(45 − 25) = 20 mm Hg and the true diastolic pressure-time index will be 8 mm Hg·sec, or only 50 percent of the calculated index. If mean coronary diastolic pressure is 95 mm Hg, the error due to the difference between diastolic left ventricular and subendocardial pressures would be smaller: The true diastolic pressure-time index would be 0.4(95 − 25) = 28 mm Hg·sec and the calculated index would be 0.4(95 − 5) = 36 mm Hg·sec; the true index is only 22 percent too low. In most of the experimental work done to relate the DPTI:TTI ratio to relative subendocardial blood flow, the low DPTI:TTI ratios were usually achieved with low mean coronary arterial diastolic pressures so that the differences between true and calculated diastolic pressure time index might have been great. This does not affect the predictive value of the DPTI:TTI ratio when coronary diastolic pressures are low; in effect, there is merely a change of scale. What is important, however, is that these empirical relations probably do not hold when coronary diastolic pressures are normal or high.

Minimal coronary vascular resistance and subendocardial flow: For subendocardial flow per gram to be proportional to the diastolic pressure-time index, the minimal resistance must be constant, but this is not always true. It may be increased by myocardial edema that occurs sometimes during cardiopulmonary bypass[16] or in hemorrhagic shock[17]; the increased myocardial water compresses intramyocardial vessels so that they cannot dilate fully.[17] Damage to coronary arteries by collagen vascular disease or their occlusion by atheroma, emboli or thrombi will also increase minimal coronary resistance. In dogs with experimental left

ventricular hypertrophy, the minimal coronary resistance is increased, although the mechanism of this increase has not been determined.[18,19] In patients with coronary artery disease reflex coronary vasoconstriction may occur.[20] Finally, it is possible that minimal resistance can also be altered by changes in ventricular size or geometry, as demonstrated in the heart perfused by high calcium perfusates.[21] In all of these instances, the rise in minimal resistance will result in lower subendocardial blood flow at any given diastolic pressure-time index. When hypertrophy has taken place before or just after birth there might be a compensatory increase in myocardial vasculature that keeps minimal resistance low; Archie et al.[22] studied newborn lambs with banded pulmonary arteries and found that minimal coronary resistance was normal in the face of marked right ventricular hypertrophy.

Blood viscosity and subendocardial flow: An increase in blood viscosity, as in polycythemia or hyperviscosity syndromes, would be expected to decrease subendocardial flow at any given diastolic pressure-time index when vessels are maximally dilated, because then minimal resistance would be elevated by the viscosity. We found this in our current studies. However, the matter is complicated by the fact that in polycythemia decreased flow does not necessarily mean a decreased oxygen supply because there is an increased oxygen-carrying capacity. Our uncompleted studies on this subject show that the effect of increased viscosity in reducing flow outweighs the increase in oxygen-carrying capacity when there is maximal vasodilatation so that subendocardial ischemia occurs at a higher diastolic pressure-time index when there is polycythemia than when there is a normal hematocrit. What is even more important than polycythemia is anemia because it is so much more common. In anemia the coronary vessels dilate and resistance decreases[23] so that at any given value of the diastolic pressure-time index the vessels are closer to maximal vasodilatation than they would be in dogs with a normal hematocrit; therefore, pressure dependency occurs at higher than expected values of the diastolic pressure-time index. To allow for this, Brazier et al.[24] converted the diastolic pressure-time index, an index of flow, into an index of oxygen supply by multiplying this index by arterial oxygen content (CaO_2) in $ml \cdot dl^{-1}$. The effect of this on the inner:outer ratio will be discussed in detail.

Systolic Pressure-Time Index (SPTI)

Sarnoff et al.[2] established the close relation of the area under the left ventricular pressure curve in systole to left ventricular oxygen consumption. They recognized that it was really wall tension that should be measured, not merely pressure, and subsequently McDonald et al.[25] confirmed that wall tension was very closely related to myocardial oxygen consumption. (In fact, both in that reference and others on the subject it is wall stress that is measured, even though it is often termed tension.) Because the pressure curve does not tell us what tension is unless we also know the ventricular radius and wall thickness, it is better to refer to the area under the left ventricular pressure curve in systole as the systolic pressure-time index (SPTI) to reinforce the fact that we do not actually estimate tension.

Systolic pressure-time index as an estimate of myocardial oxygen consumption: There are many problems in using the systolic pressure-time index to estimate myocardial oxygen consumption. First, we are most interested in subendocardial oxygen consumption, and we do not know if subendocardial and total left ventricular oxygen consumption per gram are the same. They probably change in the same direction and perhaps by the same magnitude, but actual values are not known. Second, the area under the pressure curve may be measured in different ways. Many people measure the area up to the closure of the aortic valve, thus excluding the isometric relaxation phase from the area. This makes slight difference to the total area because the area during the isometric phase is only about 5 to 10 percent of the total. In fact, because Monroe[26] found that about 85 percent of the left ventricular oxygen consumption was used by the time of peak systole, it may not be necessary to measure the whole area under the curve. This probably explains why peak systolic pressure itself correlates well with left ventricular oxygen consumption and is the basis of many of the double product values (systolic pressure times heart rate) used in human studies.[27,28] In fact, most studies that have evaluated the relation of myocardial oxygen consumption to either the systolic pressure-time index or the product of systolic pressure and heart rate have found a better correlation with the latter, especially when systole is prolonged by administering propranolol.[29] Furthermore, even the better correlations show quite wide individual variability, with a coefficient of variation of 15 percent, that is, with 5 percent of the individual values being more than 30 percent above or below the mean value for the group.

Ventricular dilatation and hypertrophy and myocardial oxygen consumption: If there is acute dilatation, then the expected myocardial oxygen consumption should increase because stress in the wall rises according to the modified Laplace formula: wall stress = radius × pressure/twice wall thickness. With acute dilatation, at any pressure the radius is greater and the wall thickness less, so that systolic pressure-time index will underestimate myocardial oxygen consumption. If there is left ventricular hypertrophy due to aortic stenosis, for example, then the wall is thicker and, in a steady state, the wall stress per unit of muscle is normal.[30] Therefore oxygen consumption per gram and flow per gram might well be normal. Recently, Cooper et al.[31] noted in experimental pressure overload hypertrophy that myocardial oxygen consumption was inefficient, that is, that the muscle used more oxygen than expected from the tension. Whether this occurs in man is unknown.

Contractility and myocardial oxygen consumption: Contractility is another important determinant of myocardial oxygen consumption. In isolated muscle strips, oxygen consumption at maximal catecholamine stimulation is about 50 percent more than expected

from the tension generated.[32] In the intact heart, however, sympathetic stimulation diminishes ventricular volume, which decreases wall stress and oxygen consumption. The sum of these two effects is to increase myocardial oxygen consumption about 25 percent per unit of systolic pressure-time index at maximal sympathetic or catecholamine stimulation in the whole heart.[33] Estimates of myocardial oxygen consumption will therefore have to be raised if there is inotropic stimulation by catecholamines or digitalis glycosides, and lowered if inotropy is depressed by beta adrenergic blockade, for example.

The DPTI:SPTI Ratio

DPTI:SPTI ratio related to inner:outer flow ratio: In our original study,[1] we observed that the inner:outer flow ratio began to decrease once the DPTI:SPTI ratio fell below a range of 0.5 to 0.8, and a representative value of 0.7 has been the basis of several clinical interpretations of myocardial blood flow. We believe now that a more correct figure to choose for the critical value below which the inner:outer flow ratio begins to decrease is 0.4 to 0.5. The evidence for this may be summed up briefly. In dogs with a Gregg cannula in the left main coronary artery it was possible to keep left ventricular pressure and systolic pressure-time index constant and to lower progressively coronary pressure and diastolic pressure-time index; in these studies[14] the critical DPTI:SPTI ratio was about 0.4 to 0.5. In a different model, Achtel et al.[34] recently showed that, when a ductal shunt was made progressively larger in the neonatal lamb, the value of DPTI:SPTI below which the inner:outer flow ratio decreased was about 0.45. Griggs and Chen[35] showed that in dogs with experimental aortic insufficiency, the subendocardial lactate:pyruvate ratio began to rise when aortic and left ventricular pressures gave a ratio equivalent to a DPTI:SPTI ratio of 0.4. In the healthy firemen studied by Barnard et al.,[6] S-T depression on sudden maximal exercise was not seen until the DPTI:SPTI ratio was below 0.45; no S-T changes were seen with ratios over 0.60, and there were no ratios between 0.45 and 0.60.

Finally, the studies of anemia by Brazier et al.[24] also led to a critical ratio of about 0.5. Their study bears further discussion here. They observed that in dogs made anemic, with or without a supravalve aortic stenosis, there was a poor correlation of DPTI:SPTI with the inner:outer flow ratio. This was due to the fact, mentioned previously, that at a given DPTI:SPTI ratio, the coronary vessels are more dilated with anemia than when the hemoglobin concentration is normal. Brazier et al. converted the measure of flow (diastolic pressure-time index) to a measure of coronary oxygen delivery by multiplying that index by arterial oxygen content (CaO_2) and introduced the myocardial oxygen supply demand ratio (DPTI $\times$ CaO_2):SPTI. When this was done, the dispersed points relating DPTI:SPTI at the inner:outer flow ratio became more orderly, and the critical value at which the inner:outer flow ratio began to fall was about 8 to 10 for the oxygen supply-demand ratio. If we take the normal arterial oxygen content as 20 ml·dl^{-1}, then we can convert this critical oxygen supply:demand value to a critical DPTI:SPTI value when hemoglobin concentration is normal by dividing it by 20; this gives 0.4 to 0.5 for the critical DPTI:SPTI value. In our original study[1] some of the dogs were moderately anemic, either spontaneously or because of blood loss during surgery. Because at that time the importance of the hemoglobin level was not appreciated, the so-called normal curve included some anemic dogs whose inner:outer flow ratio fell at a DPTI:SPTI level higher than 0.5.

Effect of occlusive coronary artery disease: If there is severe occlusive coronary artery disease, then the pressure in the coronary artery beyond the obstruction will be less than aortic pressure, and it will generally not be possible to compute the diastolic pressure-time index for the region supplied by that coronary artery. All that can be stated is that the true coronary diastolic pressure time index will be lower than that in the aorta, and that a low DPTI:SPTI ratio calculated from the aortic pressure will be even lower beyond the obstruction. Furthermore, because collateral supply to the ischemic region requires a high aortic driving pressure,[36] any fall in aortic DPTI:SPTI ratio will impair collateral flow and further jeopardize the viability of the ischemic region. Because the DPTI:SPTI ratio determines flow to the myocardium supplied by the remaining normal coronary arteries (unless there is triple vessel disease), it may influence the cardiac response when part of the heart has been infarcted.[5]

The Inner:Outer Flow Ratio

In normal dogs the inner:outer (endocardial:epicardial) flow ratio varies from about 0.8 to 1.2: It has usually been higher in conscious dogs with slow heart rates than in anesthetized dogs with tachycardia. The original reason for using this ratio rather than the subendocardial flow per gram alone was to obtain an estimate of what the heart required. For example, the normal subendocardial flow per gram at rest is about 100 ml·min^{-1}·100 g^{-1}. With severe supravalve aortic stenosis the flow might rise to 200 ml·min^{-1}·100 g^{-1} but there is still evidence of ischemia,[1] and this occurs because perhaps as much as 300 ml·min^{-1}·100 g^{-1} is needed. We therefore argued that because subepicardial flow is not restricted by myocardial compression in systole it can receive the flow that it needs under most circumstances; recently, Rouleau et al.[14] have confirmed that autoregulation remains in the subepicardial vessels after it has been exhausted in the endocardial vessels. Thus, the subepicardial flow per gram is an index of how much the heart needs for a given work load. If the subendocardial flow per gram remains about equal to the subepicardial flow per gram then presumably the subendocardium is receiving enough flow for its needs, but if the inner:outer ratio falls well below 1 then presumably the subendocardial muscle is ischemic.

Inner:outer ratio as an index of subendocardial ischemia: This interpretation must be made with caution. We do not know at what inner:outer flow ratio ischemic changes occur. If the ratio falls from its control value of 1.0 to 0.9 there will probably not be ischemia because the oxygen extraction of coronary blood can be

increased. However, the ability to compensate for decreases in flow by increases in oxygen extraction is more limited in the coronary bed than in other vascular beds. The studies of Griggs and Chen[35] and Griggs and Nakamura[37] show that the subendocardial lactate:pyruvate ratio began to rise at a DPTI:SPTI ratio (or its equivalent in those studies) that would have caused only a slight decrease in the inner:outer flow ratio. Under certain circumstances, too, the normal inner:outer flow ratio may be above 1. For example, when there is ventricular fibrillation, the inner:outer ratio may rise to 1.5[38]; therefore if in some studies with fibrillation the flow ratio is 1.0, that probably represents subendocardial ischemia, an interpretation that is supported by the finding of myocardial production in such hearts and poor cardiac function after defibrillation.[38] Finally, the inner:outer ratio is a useful way of evaluating subendocardial blood flow only if there is still some autoregulatory reserve in the subepicardial vessels. If, for example, a vasodilator is given that maximally dilates all coronary vessels, then the inner:outer ratio does not indicate whether the subendocardial muscle is receiving an adequate blood supply because now the subepicardial flows can no longer be regarded as indicating what the heart requires.

Clinical Implications

The concept of relating myocardial oxygen supply to its demand is fundamental to evaluating coronary blood flow and myocardial function, and the DPTI:SPTI is one simple way of doing this. The ratio is founded on well known physiologic principles but needs to be applied with caution and with full knowledge of its limitations. For the present we suggest the following approach to its use in patients.

Myocardial oxygen supply:demand ratio: First, it is better to use the myocardial oxygen supply:demand ratio (DPTI × CaO_2):SPTI than the DPTI:SPTI ratio because the former corrects for changes in arterial oxygen content. It is likely that arterial hypoxemia will also be taken into account by the oxygen supply:demand ratio, although definitive experiments have not yet been done. If the hemoglobin concentration is normal, then either ratio can be used. Current studies in normal dogs indicate that the critical ratio is about 0.4 to 0.5 for DPTI:SPTI or about 8 to 10 for (DPTI × CaO_2):SPTI. These ratios are likely to be of most use when mean coronary diastolic pressures are low, as in patients with low output states or aortic incompetence. If mean coronary diastolic pressures are normal or high then at present the usefulness of these pressure ratios is in doubt.

Values of the oxygen supply:demand ratio below the critical level are likely to be associated with a reduced relative subendocardial blood flow and oxygen supply. Small changes in the supply:demand ratio can be met by increased oxygen extraction, but greater reductions in the ratio probably do cause myocardial ischemia.

Effect of increased coronary vascular resistance: If there is reason to believe that coronary vascular resistance is increased—as in polycythemia, macroglobulinemia, myocardial edema or hypertrophy—then the critical supply:demand ratio will be higher. Unless the minimal coronary vascular resistance can be measured or estimated, there is no way of knowing what the critical ratio will be. Under these circumstances, the myocardial oxygen supply:demand ratio can be used only to set a lower limit. If the critical ratio is 8 to 10 with a normal minimal coronary vascular resistance, a ratio of 10 is likely to be inadequate for subendocardial oxygen supply when minimal coronary vascular resistance is raised. Therefore in practice it would be wise to attempt to achieve ratios well above 10 in order to optimize subendocardial blood flow.

Effect of inotropic stimulation: If there is marked inotropic stimulation of the heart then the systolic pressure-time index will tend to underestimate myocardial oxygen needs. It seems as if at worst the underestimate is about 25 percent, so that the critical myocardial oxygen supply:demand ratio will rise from 8 to 10 to about 10 to 12.5 when there is marked inotropic stimulation. If there is acute ventricular dilatation then once again the systolic pressure-time index will underestimate myocardial oxygen needs. Echocardiography may allow us to approximate this change in ventricular radius and so include it in our calculations. As a rough guide, for each unit of systolic pressure-time index, myocardial oxygen consumption will go up in proportion to the increase in ventricular radius above its normal value.

Effect of coronary arterial obstruction: When there is coronary arterial obstruction, then the pressure ratio that is related to subendocardial flow in the region supplied by that artery is not usually known, so that localized subendocardial ischemia cannot be predicted by these ratios. However, they can be used at surgery to help assess the adequacy of graft flow.[10] Furthermore, the ratios can also be used as limits, in that a ratio that is low for normal hearts is probably lower still for a region supplied by a stenotic artery. In addition, collateral flow will be jeopardized by too low a pressure ratio since the resistance of coronary collateral vessels, at least in dogs,[39] is higher than normal.

With these rough guidelines it should be possible to use the supply:demand ratio to assess what is happening in patients, at least directionally, in sequential studies. As more precise physiologic studies of the ratio are made, it should be possible to be more accurate in deciding what is occurring to subendocardial blood flow and oxygen supply.

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Group Teaching of Auscultation

Use of a New Wireless Stethoscope-Type Headphone

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A new technique using infrared light for the transmission of heart sounds and murmurs is described. This method enables the simultaneous transmission of heart sounds and murmurs to large groups of persons without the need for hard-wire connections to the amplifying device. The method facilitates teaching of cardiac auscultation at the bedside as well as in the setting of conferences, seminars or postgraduate education programs.

The clinician who deals with the diagnosis and assessment of various forms of heart disease now has an impressive list of diagnostic tools to use. The electrocardiogram, vectorcardiogram, phonocardiogram, echocardiogram, chest X-ray film and cardiac catheterization procedures are among the commonly used aids. Because these sophisticated diagnostic tools have enhanced our understanding of the pathophysiology of many forms of heart disease, cardiac auscultation using the lowly stethoscope has become an even more valuable diagnostic tool. In many instances, adequate, reliable cardiac auscultation integrated with a solid working knowledge of the pathophysiology of cardiac abnormalities provides most of the information necessary for accurate diagnosis and assessment.

Drawbacks of Available Teaching Aids for Cardiac Auscultation

The continuing and even increased usefulness of the stethoscope as a diagnostic aid underlines the need for more efficient and reliable methods of teaching cardiac auscultation. Such methods are needed not only for educating medical students in the use of the stethoscope but for training house officers and providing continuing education for physicians. Several aids for teaching cardiac auscultation—recorded tapes, records and heart sound simulators, for example—have been developed, and progress has been considerable since the use of the first "listening post" using a reel-to-reel tape recording and a dynamic speaker.[1] Nevertheless, these sophisticated aids cannot truly match the efficacy of learning directly from the patient at the bedside when there is a one to one relation between teacher and student. This traditional method of using the stethoscope for teaching cardiac auscultation does have its drawbacks.[2] The number of medical students, house officers and physician students exceed the number of available teachers so that group teaching is now commonly utilized. The practice of having each student in the group take turns listening to the patient is time-consuming and inefficient for teaching transient auscultatory phenomena such as the diastolic murmur of mitral stenosis brought out only by maneuvers such as coughing or turning, the change in murmur intensity with squatting or the Valsalva maneuver in idiopathic hypertrophic subaortic stenosis or mitral valve prolapse.

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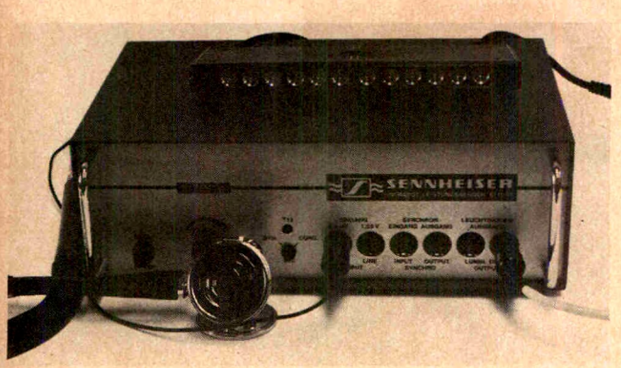


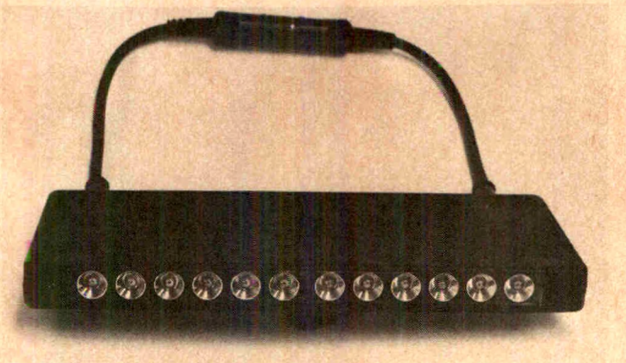
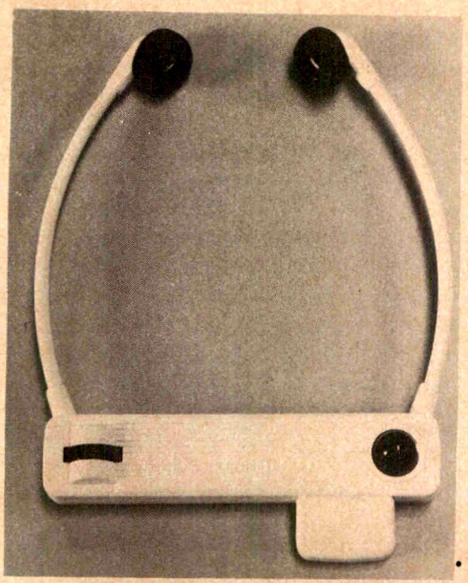


FIGURE 1 (left). The Sennheiser amplifier. The stethoscope-microphone transducer and infrared transmitter are shown appropriately connected.
FIGURE 2 (right). Infrared monotransmitter model SJ-1010 industrial unit.

In recent years this problem was solved by the use of electronic stethophones. A microphone was used to pick up the auscultatory event and, with the use of an amplifier, the sound was transmitted to stethophones for simultaneous group listening. In order to duplicate more closely and teach the use of the various stethoscopic pieces, we have utilized the regular stethoscopic heads as the primary chest "pickup," transmitting the sound to a microphone for amplification. However, this method of teaching also has some drawbacks. For group teaching at the bedside, appropriate connecting wires and junction boxes have to be provided so that each student can plug in his stethophone. This often results in crowding around the patient's bed where the junction box may be most conveniently placed. Setting up and gathering these connection wires and junction boxes, as well as plugging and unplugging these stethophones as one moves from one patient room to another, uses up valuable time. Furthermore, the multitude of wires can serve as an antenna and pick up extraneous events such as electrical interference and at times, even a hospital's paging system. To teach large groups in a conference room or auditorium, one either has to lay out the interconnecting wires to permit a stethophone to be



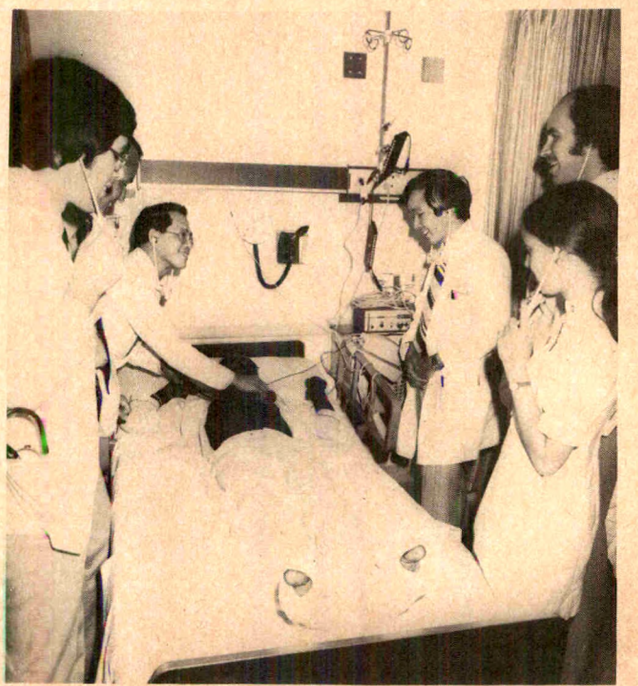


FIGURE 3 (left). Monaural unit SJ 406. On the left side of the unit is an off-on volume control and on the right side (circular bulb-like), the infrared receiver. At the bottom right is a plug-in rechargeable battery capable of 5 hours of continuous use.
FIGURE 4 (right). Bedside use of the infrared system. Only the microphone-stethoscope assembly needs to be on the patient's bed. The amplifier is on the bedside table and the infrared transmitter is attached to a pole for intravenous feeding.

FIGURE 5. Group auscultation in the setting of a large conference or classroom.

plugged in at each seat or one must perform the costly procedure of wiring and installing permanent stethophone outlets at each seat. These physical requirements also limit the teaching of auscultation in hospitals other than one's own institution.

New Bedside Method for Teaching Auscultation

Recently, we have tested and used a new method for group teaching that overcomes many of these drawbacks using "off the shelf" electronic components. As in our earlier work, a stethoscopic head is used as the primary pickup, and the appropriate heart sounds and murmurs are transmitted through a Sennheiser microphone* connected to an amplifier transmitter (Fig. 1). However, the auscultatory event is not transmitted by hard wire but by infrared light (Fig. 2).† Specially designed headphones (stethophones) (Fig. 3)‡ receive the signal without need for a direct wire connection. Each of these elements in the system has a characteristic frequency response. When the pressure transducer is coupled with the stethoscopic head, the high frequency response is acoustically padded to reduce high frequency noise. Most of the audible cardiovascular events in health and disease fall in the frequency range of 20 to 1,000 cycles/sec. The system (without the damping effect of the stethoscopic head and tubing) has

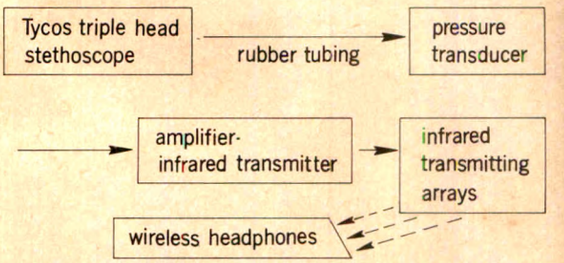


FIGURE 6. Diagram of auscultation teaching system.

a flat response from 20 to 3,000 cycles/sec. The addition of the regular stethoscope to the system not only reduces the high frequency noise but also closely reproduces the characteristic timbre and quality of heart sounds and murmurs that one appreciates at the bedside during routine auscultation with the stethoscopic bell and diaphragm. The quality of sound reproduction is excellent and the individual headphone volume control also allows each student to adjust volume to suit his or her needs. This allows for individual adjustment to achieve the threshold of audibility especially for low frequency events. Because no wires are involved, the system is not subject to electrical interference. The sounds can be transmitted and appropriately received so long as the infrared beam can be received; thus, good reception can be obtained for distances of 500 yards or more.

We have used the system at the bedside for teaching both students and house staff officers and have found it effective and simple to use. The set-up time is substantially reduced and there is no crowding around the patient's bed (Fig. 4). The system is equally effective in large auditoriums and simply requires the positioning of an adequate number of infrared transmitters. Its portability has been a real asset and has also been effectively used in mobile teaching units and teaching conferences (Fig. 5).

The entire system can be diagrammed as shown in Figure 6.

The one potential drawback of the system is that infrared emission from other sources may interfere with the signals. Thus, it cannot be used outdoors because the sun's infrared rays interfere. Indoors, the amount of infrared rays from standard room lighting and applicances is sufficiently great to cause interference.

The use of an infrared beam as a mode of transmission for sound and physiologic events opens up the potential for transmission also of the electrocardiographic signal and of palpatory events as well. Its potential value in teaching is suggested by our success in using it for sound transmission.

* Model MK-E-9 Sennheiser pressure transducer, using an Elekret element.

† Infrared monotransmitter model SI-1010 industrial unit.

‡ Monaural unit SI-406 with rechargeable batteries good for 5 hours of continuous use.

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Successful Treatment of Drug-Resistant Atrial Tachycardia and Intractable Congestive Heart Failure With Permanent Coupled Atrial Pacing

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Temporary coupled atrial stimulation slowed the ventricular rate by nearly 50 percent in an adolescent patient with intractable congestive heart failure and focal repetitive atrial tachycardia that was resistant to drug treatment. Because of the success with the temporary pacemaker, a specially designed permanent pacemaker was implanted to provide coupled atrial stimulation. The necessary electrophysiologic conditions for ventricular slowing by coupled atrial pacing are: (1) an atrial effective refractory period shorter than that of the atrioventricular junction, and (2) depolarization of the ectopic atrial pacemaker by the responses to coupled atrial stimulation. During a 4 year follow-up period the treatment resulted in elimination of the tachycardia, followed by return of the heart size to normal and complete clinical recovery. Coupled atrial stimulation can provide effective treatment in selected patients with disabling drug-resistant atrial tachycardia in whom this mode of therapy is shown to be effective by careful electrophysiologic studies.

Chronic repetitive or persistent supraventricular tachycardia is frequently resistant to treatment with antiarrhythmic drugs,[1–5] and, when associated with a rapid ventricular rate, may produce congestive heart failure,[1,2,6–11] cardiomegaly and even death.[12–14] Indeed, surgical interruption of the atrioventricular (A-V) conduction system[15–17] and ablation of atrial tissue surrounding the ectopic focus[18] have been resorted to in patients with refractory supraventricular tachycardia and severe chronic congestive failure.

We describe here the successful treatment of an adolescent patient with severe congestive heart failure associated with repetitive drug-resistant supraventricular tachycardia by a specially designed implantable pacemaker for coupled atrial stimulation. A preliminary account of this patient has been reported previously.[19]

Case Report

A previously well 17 year old white youth had an episode of sore throat, cough, headache, vomiting, palpitations and dizzy spells lasting 3 days in June 1971. One month later he experienced palpitations, weight loss, malaise, sharp non-radiating left chest pain and recurrent syncopal episodes. During the next year, he was hospitalized numerous times in other institutions for diagnostic studies including comprehensive cardiac evaluation. His heart rate ranged between 140 and 180 beats/min; a grade 3/6 pansystolic apical murmur radiating to the axilla was heard. Electrocardiography revealed repetitive supraventricular tachycardia, premature ventricular beats, left atrial enlargement and severe left ventricular hypertrophy and strain. Chest roentgenography revealed cardiomegaly. Endomyocardial biopsy disclosed increased lipochrome pigment. Skeletal muscle biopsy tissue was normal on light and electron microscopy. Complement fixation tests for respiratory viral antigens yielded inconclusive results.

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Cardiac catheterization during tachycardia (140 to 160 beats/min) revealed no shunts, a large arteriovenous oxygen difference and a cardiac index of 1.5 liter/min per M^2. The recorded pressures are listed in Table I. Angiography revealed a markedly dilated and poorly contracting left ventricle. The aortic valve, ascending aorta and coronary vessels were normal. Minimal mitral regurgitation into a slightly dilated left atrium was noted. The diagnosis was congestive cardiomyopathy of undetermined etiology associated with chronic supraventricular tachycardia. Bed rest in a hospital for 6 months did not improve the patient's condition. Digoxin, propranolol, quinidine, procainamide and phenytoin in various doses and combinations did not alter the tachycardia. The patient's prognosis was considered grave, and his family was told that his life expectancy was limited.

The first admission of this patient to Michael Reese Hospital was in January 1973. Physical examination revealed a pale patient 190 cm tall, weighing 61 kg. Blood pressure was 100/70 mm Hg. Heart rhythm was slightly irregular at a rate of 140 beats/min. A left ventricular impulse was present in the seventh intercostal space at the anterior axillary line. A grade 3/6 apical holosystolic murmur radiating to the axilla was present. The electrocardiogram (Fig. 1A) revealed a repetitive supraventricular tachycardia. The ectopic P waves were inverted in leads II, III and aVF with a P-R interval of 0.14 second, suggesting a low atrial origin of the impulse. The first ventricular complex shown in Figure 1A was the last beat of a run of tachycardia; the run was followed by a pause of 0.96 second terminated by a single sinoatrial P wave that conducted to the ventricles after a normal P-R interval. The tachycardia typically restarted after this sinus beat at a cycle length of 0.56 second and gradually accelerated before coming to an end. The average rate varied between 130 and 160 beats/min. Frequent premature ventricular beats occurred, usually followed by compensatory pauses. A pattern of left ventricular hypertrophy and strain was present. Chest roentgenography disclosed cardiomegaly and a globular-shaped heart. The arrhythmia and heart failure were not significantly affected by treatment with digoxin (0.75 mg/day) and procainamide (2 g/day). Propranolol (420 mg/day) slowed the rate to 110 beats/min and produced second degree atrioventricular (A-V) block with Wenckebach periods.

Electrophysiologic Studies

Intracardiac records during the arrhythmia showed a P-H interval of 75 msec and an H-V interval of 53 msec. Intravenous infusion of isoproterenol (0.5 μg/min) accelerated the ectopic rate from 140 to 167 beats/min (Fig. 1B). Right atrial pacing at rates of 90 to 110 beats/min produced competitive pacing; stimuli that captured the atria did not stop the tachycardia but usually reset its cycle. Atrial drive at rates of 120 to 180/min suppressed the tachycardia, but all these impulses conducted to the ventricles. Upon cessation of atrial drive, the tachycardia reappeared immediately at the original spontaneous rate. Atrial pacing at a rate of 400 beats/min resulted in a short-lasting episode of atrial fibrillation, with an average ventricular rate of 120 beats/min (Fig. 1C), followed by reappearance of the tachycardia. Right ventricular pacing at 130 beats/min was associated with retrograde activation of the atria and suppression of the atrial tachycardia. Slower ventricular driving rates resulted in competitive pacing and intermittent A-V dissociation in the presence of the atrial tachycardia.

TABLE I

Cardiac Catheterization Findings

Site	Pressures (mm Hg)
Right ventricle	28/4
Main pulmonary artery	30/14 (20)
Left ventricle	82/20
Aorta	80/68 (70)

Values in parentheses are mean pressures.

Using a synchronous external pulse generator, triggered by the atrial electrical activity, we delivered test pulses to the right atrium at varying intervals that scanned the atrial cycle. The atrial diastolic threshold was 1.6 milliamperes (mA). The test stimuli were of 4 mA intensity. During the tachycardia, the effective refractory period of the atrium was 180 msec, and that of the A-V junction was 300 msec. Single effective atrial test stimuli usually reset the ectopic cycle but never stopped the tachycardia.

We observed that test stimuli with the *same* coupling interval produced a longer return cycle when inserted at the beginning of a run of tachycardia, when the rate was relatively slow, than when they were inserted later in the tachycardia, when the rate was faster. When the coupling interval was *varied* between 180 and 350 msec, the return cycle was related directly to the length of the coupling interval. However, when *repetitive* stimuli with the *same* coupling interval were delivered in alternate cycles, progressive prolongation of the return cycle was noted after the first three consecutive stimuli, but thereafter the extent of prolongation remained nearly constant (Fig. 1D).

The potential therapeutic efficacy of properly timed coupled atrial stimulation in slowing ventricular rate during the atrial tachycardia becomes apparent by comparing panels A and D in Figure 1. The coupled electrical stimuli are delivered after the termination of the atrial refractory period, but early enough for the atrial responses to occur within the refractory period of the A-V junction and to be blocked there. With resetting and prolonging of the cycle of the ectopic atrial focus, the coupled stimuli result in slowing of the ventricular rate.

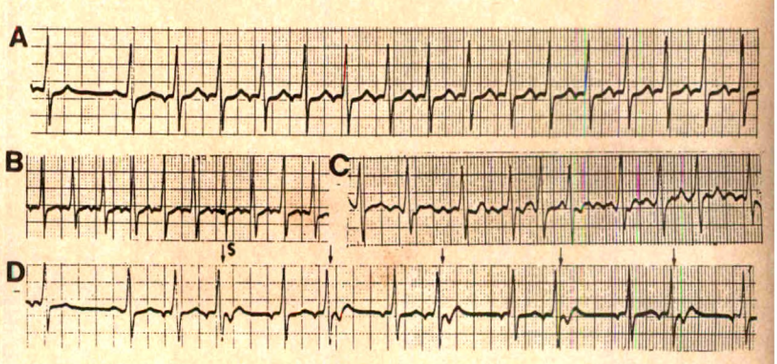

FIGURE 1. Panel A, an ectopic repetitive low atrial tachycardia (lead II). **Panel B,** intravenous infusion of isoproterenol (0.5 μg/min) resulting in regularization of the tachycardia and in acceleration of the rate from 140 to 167 beats/min. **Panel C,** atrial fibrillation with an average ventricular rate of 120 beats/min that resulted from atrial stimulation at 400 pulses/min. **Panel D,** effect of coupled electrical stimuli (S) **(vertical arrows)** delivered to the low right atrium 180 msec after alternate spontaneous P waves. They result in inverted, premature and nonconducted P waves that reset the ectopic atrial pacemaker and produce returning cycles that lengthen with repetitive stimulation. Note the nearly 50 percent prolongation in the ventricular cycle during coupled atrial stimulation (see text).

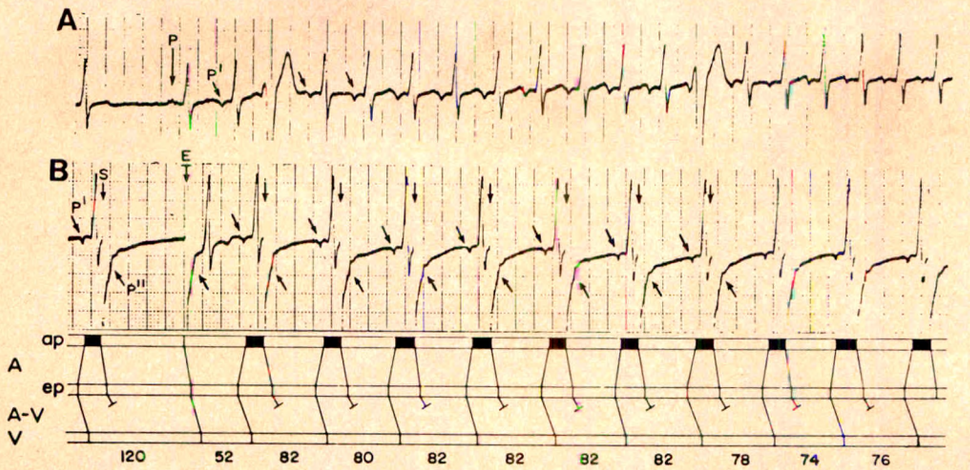

FIGURE 2. A, repetitive atrial (A) tachycardia with premature ventricular (V) beats. **B,** diagram showing how the artificial pacemaker (ap) resets the ectopic pacemaker (ep) and slows the heart. The first ventricular complex is a response to the last of a run of ectopic atrial depolarizations (P′). The latter triggers a coupled stimulus (S) resulting in a nonpropagated atrial response (P″). After the pause, an escape (E) of the artificial pacemaker occurs at its automatic interval of 910 msec, resulting in an atrial response propagating to the ventricles. Then the atrial tachycardia reappears. Each of the ectopic P′ depolarizations propagates to the ventricle but also to the site of the atrial sensing electrode, triggering the pacemaker to deliver a stimulus to the atrium after the delay interval of 180 msec (**black bars** in diagram). The atrial responses that result depolarize and reset the ectopic pacemaker but are blocked at the A-V junction, which is still refractory. Consequently, the ventricular rate slows. (Numbers are in 0.01 second.)

Therapeutic Considerations

In view of the patient's grave condition, his refractoriness to drug treatment and the proved ability of critically timed electric depolarizations of the atria to slow the heart, we considered implantation of a pacemaker for permanent coupled atrial stimulation[20] as a possible life-saving measure. Accordingly, a special pulse generator was constructed (Atricor, Cordis Corporation, Miami, Florida) with the following specifications: pulse duration 1.62 msec; current into a 500 Ω load 7.1 mA; maximal triggered rate 129.1 revolutions per minute; automatic escape rate of 65.6 pulses per minute; coupling interval between sensing and stimulation 180 msec. In preliminary studies we found that the latter interval resulted in atrial responses that were blocked at the A-V junction and produced significant slowing of the ventricular rate. Two atrial leads, one for sensing and one for stimulation, completed the pacemaker system.

Pacemaker Implantation and Postoperative Course

On March 7, 1973 a left thoracotomy was performed. The left ventricle was large, tense and poorly contracting; the left atrium was bulging and tense. The sensing atrial lead was attached high on the left atrial appendage to minimize the possibility of sensing ventricular depolarizations. The stimulating lead was attached close to the sensing one.

During the first postoperative week, the pacemaker stimuli were ineffective because of transient prolongation of the atrial refractory period induced by the operation. After the second postoperative week, the number of coupled stimuli that were effective increased. Some of the coupled responses conducted to the ventricles and accelerated the ventricular rate. This complication was controlled with the use of digoxin and propranolol to prolong the A-V junctional refractory period. Sustained coupled atrial stimulation with slowing of the ventricular rate was observed during the third postoperative week (Fig. 2). Concomitantly, long runs of sinus rhythm became frequent and alternated with progressively diminishing runs of tachycardia. On the 46th postoperative day, the resting electrocardiogram showed an escape pacemaker rhythm (Fig. 3A) because the sinus rate at rest was slower than the escape rate of the artificial pacemaker (66/min). However, after exercise (Fig. 3B), the sinus rate (79/min) exceeded the escape rate of the pacemaker and triggered the pacemaker to a coupled mode, resulting in ineffective coupled atrial stimulation. The coupled atrial stimuli were ineffective during sinus rhythm because the sinus rate was slower than the rate of the atrial tachycardia and therefore, was associated with a longer atrial refractory period. Ectopic atrial beats were not observed.

Long-Term Follow-Up

The patient has been followed up at our pacemaker clinic for 4 years. After exercise, single or multiple ectopic atrial beats punctuated the dominant rhythm during the first month after discharge from the hospital. Thereafter, the patient had either a pacemaker escape rhythm (Fig. 3A) or sinus rhythm with ineffective coupled atrial stimulation (Fig. 3B). During exercise-induced sinus tachycardia, with shortening of the atrial refractory period, coupled atrial stimulation became effective and slowed the ventricular rate by resetting the sinoatrial pacemaker (Fig. 3C). Marked symptomatic improvement occurred and the electrocardiographic signs of left ventricular hypertrophy and strain disappeared over a period of about 8 months (Fig. 3, D to G). The heart size, determined radiographically, diminished within 4 months after operation and is now normal. Physical examination no longer reveals any abnormalities except for the presence of the pacemaker. The patient has returned to normal activities.

Discussion

Several features in the behavior of the tachycardia suggested that it originated in an accelerated atrial pacemaker rather than in a reentrant circuit: The rate of the tachycardia decreased during treatment with propranolol, and it increased during infusion of isoproterenol (Fig. 1B). The tachycardia could not be interrupted with atrial or ventricular pacing. Repetitive coupled atrial stimulation during a run of tachycardia resulted in gradual lengthening of the return cycle (Fig.

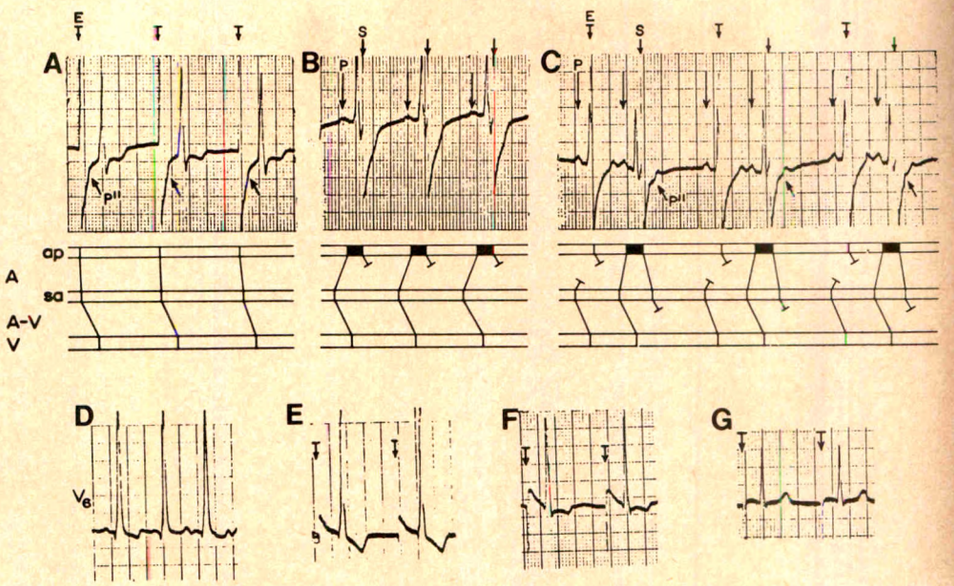

FIGURE 3. Top row, various rhythms observed after elimination of the atrial tachycardia. **A,** at rest the heart is driven by the automatic escape (E) of the artificial atrial pacemaker (ap) at a cycle length of 910 msec. **B,** sinus rhythm (P) appearing after exercise (several sit-ups) is associated with ineffective coupled atrial stimulation. **C,** bigeminal rhythm during exercise-induced sinus tachycardia at a rate of 120/min due to effective coupled atrial stimulation in alternate cycles. Each long cycle terminated by a sinus beat is followed by an ineffective pacemaker escape. **Bottom row,** lead V_6 obtained before pacemaker implantation **(D)** and 41 days **(E),** 4 months **(F)** and 23 months **(G)** after implantation. Note the gradual disappearance of signs of left ventricular hypertrophy and strain. sa = sinoatrial node; other abbreviations as in Figure 2.

1D), suggesting overdrive suppression. We elected therefore to slow the ventricular rate during the tachycardia by using the method of coupled atrial stimulation described by Langendorf and Pick[20] in 1965 as a temporary means of slowing the ventricular rate during uncontrollable sinus tachycardia. A similar technique was also reported during the same year by Chardack et al.[21] These studies followed the work of Lopez et al.,[22] who first demonstrated the feasibility of slowing the heart rate with paired atrial stimulation. Their method, which involves the asynchronous delivery of two electric pulses separated by a fixed interval, is a useful temporary technique for slowing the ventricular rate during tachycardia. For long-term treatment, however, paired atrial pacing was less desirable than coupled pacing because it would have competed continuously with the sinoatrial pacemaker.[23]

Mechanism of slowing of ventricular rate and suppression of atrial tachycardia: The proposed mechanism of slowing involved during coupled atrial pacing is shown in Figure 4. During coupled stimulation, the pacemaker is triggered by the spontaneous atrial depolarization to deliver a pulse at a preset interval. The first ectopic cycle is 400 msec long. The second ectopic atrial impulse reaches the atrial sensing electrode after time B and triggers the pacemaker to deliver a pulse after a coupling interval (CI) of 180 msec. The stimulus, delivered after the atrial effective refractory period, results in a response reaching the A-V junction after propagation time B′. It must arrive there during the A-V junctional effective refractory period in order not to propagate to the ventricles. If propagated, the coupled responses would accelerate the ventricular rate. Therefore, the first requirement for slowing of the ventricular rate by means of coupled atrial stimulation is that the sum of the atrial effective refractory period plus propagation times B and B′ be less than the A-V junctional effective refractory period. The second requirement is that the response to coupled atrial stimulation must depolarize the ectopic pacemaker and reset its cycle. In Figure 4 the return cycle length (EC) of the ectopic pacemaker was assumed to equal that of the ectopic cycle (400 msec). The ventricular cycle length during effective coupled atrial stimulation is composed of the sum of intervals B + CI + B′ + EC, measuring 700 msec. The longer the ectopic return cycle (EC), the greater the prolongation in the ventricular cycle, that is, the greater ventricular slowing (Fig. 1D). The failure of this technique to slow the ventricular rate during sinus rhythm in one of the patients of Lister et al.[24] was probably caused by the relatively longer atrial than A-V junctional effective refractory period.[25] Administration of digitalis may be helpful in such a case by shortening the atrial and lengthening the A-V junctional effective refractory period.

Clinical implications: The observation that permanent coupled atrial stimulation resulted not only in ventricular slowing but also in suppression and elimi-

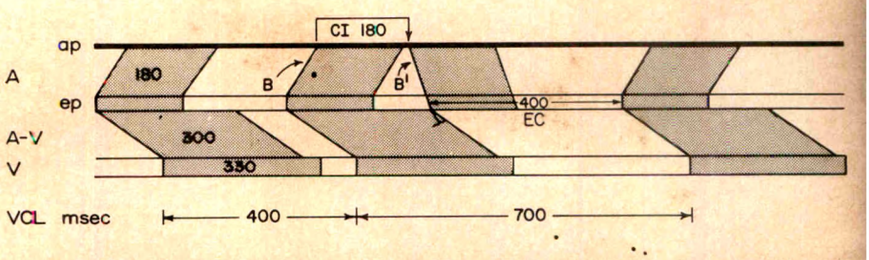

FIGURE 4. Diagram showing the mechanisms of ventricular slowing by coupled atrial stimulation during atrial tachycardia. See text for explanation. A = atrial activity; ap = position in the left atrium of the sensing and pacing electrodes for coupled atrial stimulation; A-V = atrioventricular conduction time; CI = coupling interval; EC = ectopic return cycle length; ep = low atrial ectopic pacemaker; V = ventricular activity; VCL = ventricular cycle length. The **shaded areas** represent the duration of the atrial and A-V functional refractory periods after activation.

nation of the ectopic tachycardia demonstrates the effectiveness of the technique as a method of treatment of selected cases of drug-resistant chronic ectopic atrial tachycardia. Implantation of such a pacemaker is preferable to the irreversible effects produced by operative interruption of the A-V conduction system[15–17] or to ablation of the ectopic focus.[18] The marked clinical improvement in our patient demonstrates the important if not primary role of tachycardia in producing intractable congestive heart failure. Tachycardia-induced cardiomegaly and congestive heart failure that are reversible with slowing of the heart rate have been reported in infants,[2,13,26–28] children[2,7,10,13,28,29] and adults,[6,8,9,30–32] and experimentally in dogs.[33]

The development of tachycardia and cardiac illness in our patient was preceded by a viral upper respiratory tract infection. Viral myocarditis might have been the triggering event. However, the patient's recovery after elimination of the tachycardia suggests that irreversible myocardial damage possibly induced by viral myocarditis was less important in producing heart failure than the persistent tachycardia. The association of viral myocarditis and supraventricular tachycardia has been reported.[10,34–36]

Although the prognosis of chronic supraventricular tachycardia has been regarded as generally good in some reported series,[5,26] fatalities have been reported in adolescent patients with chronic atrial tachycardia without other demonstrable heart disease.[12,14] Our patient's prognosis has greatly improved, and during the 4 years of follow-up he has had normal sinus rhythm and been asymptomatic.

Acknowledgment

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Use of a Double Atrial-Triggered Standby Pacemaker System For a Patient With a Biventricular Bypass Heterotopic Cardiac Homograft

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In a patient who had a biventricular bypass heterotopic cardiac homograft a double atrial-triggered standby pacemaker system was implanted to allow sequential atrial pacing of both hearts. The system design permitted either the recipient or the donor heart to dictate the rate of its fellow, depending on which heart had the faster spontaneous sinus rate at any time. Alternative methods for achieving sequential pacing are discussed.

Biventricular bypass transplants have become the preferred method of cardiac transplantation at our institution over the past few years. The initial technique, previously described in detail,[1] has since been modified to allow bypass of both the right and the left ventricle of the failing recipient heart by the implanted donor heart. Briefly, the homograft heart is implanted in the chest to the right of the recipient's own heart. Both atria and the aorta of the donor heart are anastomosed to their equivalent recipient heart structures. A graft is used to link the pulmonary artery of the donor heart to that of the recipient heart. Postoperatively this technique has produced excellent hemodynamic improvement and a smoother recovery than conventional orthotopic cardiac transplantation. Postoperative hemodynamic studies[2] have shown that the donor heart left ventricle assumes the major pumping function in the face of a noncompliant poorly contracting recipient left ventricle. However, because the recipient left ventricle has been shown to eject more effectively when it contracts out of phase with the donor left ventricle,[2] we implanted a permanent pacemaker system in a patient to allow donor and recipient hearts to contract sequentially.

Case Report

The patient was a 35 year old man who had had a myocardial infarction the previous year. He presented with progressive symptoms of biventricular cardiac failure despite optimal therapy. Cardiac catheterization confirmed severe cardiac failure with a resting left ventricular diastolic pressure of 38 mm Hg. Angiography revealed a dilated hypokinetic left ventricle as well as proximal obstruction of the left anterior descending and right coronary arteries with a nonobstructed but diffusely diseased left circumflex vessel.

At the time of cardiac transplantation a unipolar Cordis "9-turn" epicardial electrode was attached to the left atrium of the donor heart, while another electrode was attached to the left atrium of the patient's own heart. The donor heart electrode was connected to a specially modified Cordis Ectocor R wave-triggered pacemaker and the recipient heart electrode to a single-terminal modified Cordis Atricor pacemaker. Both pacemakers were implanted subcutaneously beneath the left costal margin in the anterior abdominal wall.

The donor heart pacemaker had a refractory period of 400 msec and an alert period of 460 msec with a total cycle of 860 msec, giving a standby rate of 70/min,

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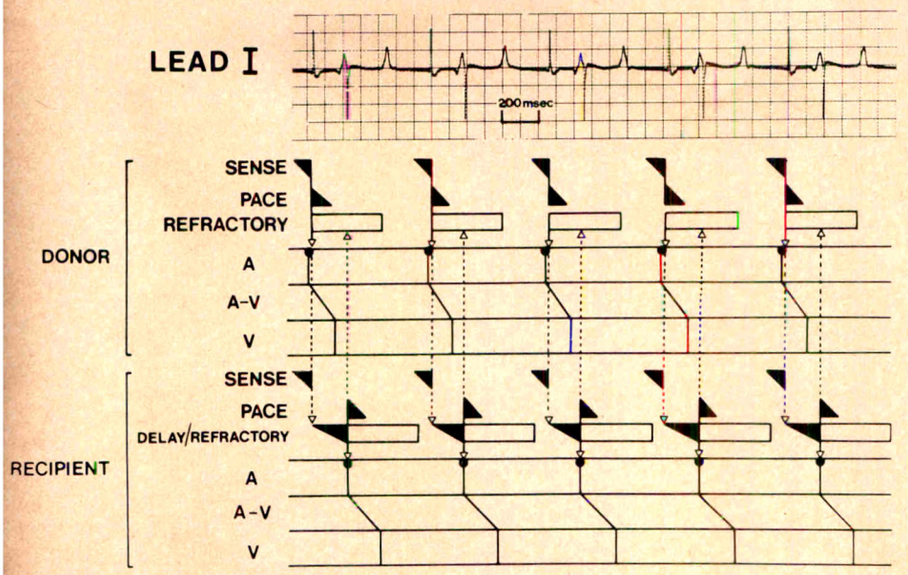

FIGURE 1. Electrocardiogram and ladder diagram illustrating operation of the two pacemakers when the spontaneous donor sinus rate exceeds that of the recipient heart (see text).

which is standard for a Cordis Ectocor standby pacemaker. However, the pacemaker's sensitivity for R wave recognition was increased to 1.0 mv to allow detection of the donor P wave. The recipient pacemaker was a Cordis Atricor pacemaker modified to operate with a common sensing and pacing electrode. It had a poststimulation refractory period of 360 msec, an alert period of 310 msec and an increased sensing to stimulation delay period of 180 msec. This postsensing delay plus a physiologic latency period of approximately 40 msec determined the time between atrial systole of donor and recipient hearts, and the postsensing delay period was chosen to be less than the expected electrical refractory period of the recipient atrium.[3,4]

Figure 1 shows a postoperative electrocardiogram recorded when the donor heart had a spontaneous sinus rate above that of the spontaneous recipient sinus rate. Donor pacemaker spikes are positive, and recipient spikes are negative. A spontaneous donor P wave provokes an immediate discharge from its pacemaker. The donor QRS complex follows at a P-R interval of 150 msec and is distorted in its terminal portion by the recipient pacemaker spike. The donor pacemaker spike is sensed by the recipient pacemaker and, after a 180 msec delay, the recipient pacemaker fires, stimulating the recipient atrium. The resulting recipient P wave is followed 180 msec later by a QRS complex.

Figure 2 shows an electrocardiogram recorded when the recipient sinus rate was faster than that of the donor heart. A spontaneous P wave of the recipient heart is sensed by its pacemaker, which fires 180 msec later. Because this occurs within the electrical refractory period of the recipient atrium, the pacemaker stimulus fails to induce a further P wave. The recipient P wave is followed by a QRS complex at a P-R interval of 170 msec. The recipient pacemaker spike is sensed by the donor pacemaker, which immediately fires, producing

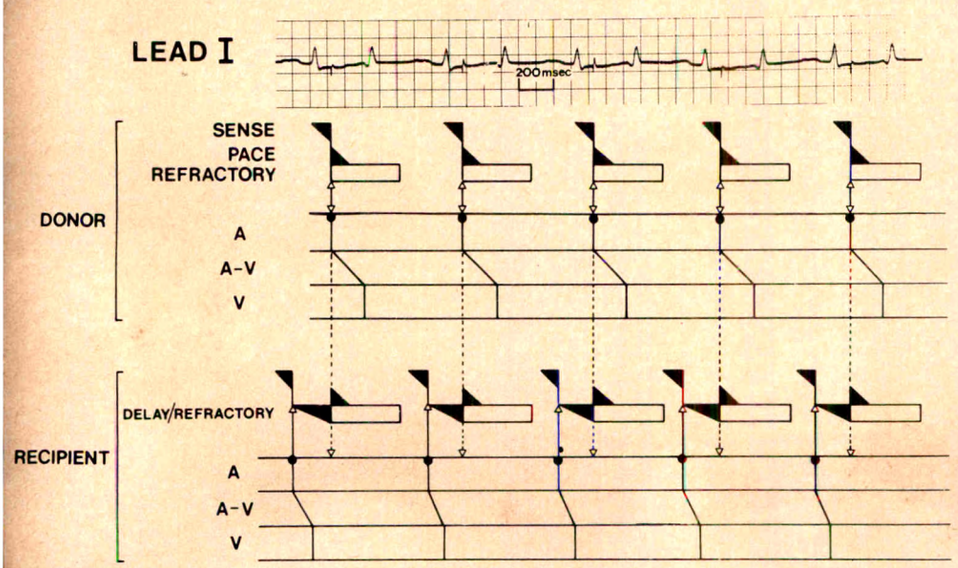

FIGURE 2. Electrocardiogram and ladder diagram illustrating operation of the two pacemakers when the spontaneous recipient sinus rate exceeds that of the donor heart (see text).

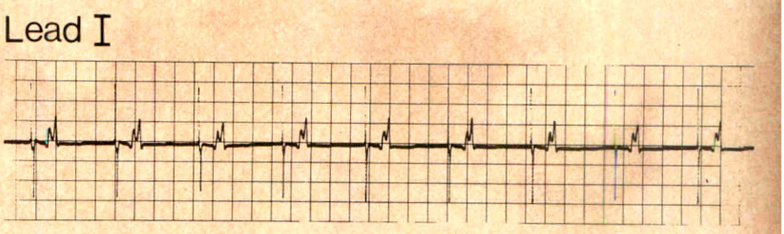

FIGURE 3. Electrocardiogram illustrating situation in which the sinus rate of both donor and recipient hearts has fallen below the standby rate of both pacemakers (see text). (Paper speed 25 mm/sec.)

a P wave in the donor electrocardiogram, followed by a QRS complex at a P-R interval of 150 msec. Because both pacemakers fire in quick succession, the pacemaker spike appears single and biphasic because of the combination of the positive donor and negative recipient pacemaker spikes.

Discussion

Benefits of sequential contraction of donor and recipient hearts: Although postoperative hemodynamic studies were not performed in this patient, postoperative catheterization findings in two other patients without a pacemaker system have demonstrated the potential benefit of sequential contraction of the donor and recipient hearts.[2] These studies showed that systole of the recipient left ventricle was isovolumic when it occurred synchronously with systole of the healthier donor left ventricle, probably because of the relative underfilling of the noncompliant recipient left ventricle when it had to compete for filling with the healthier more compliant donor left ventricle. This underfilling caused the recipient left ventricle to fail to generate a high enough peak systolic pressure to open its aortic valve. The aortic pressure generated by the healthier donor left ventricle exceeded the maximal systolic pressure that could be generated by the underfilled poorly contracting recipient left ventricle and also contributed to its failure to eject when the donor and recipient ventricles filled and contracted synchronously. When systole of the recipient left ventricle occurred well after systole of the donor ventricle, competitive diastolic filling was minimized, and aortic pressure decreased sufficiently to allow the recipient ventricle to attain higher end-diastolic and systolic pressures and thus open its aortic valve and eject blood.

The optimal delay between donor and recipient left ventricular systole was not determined for our patient but, for the reasons explained earlier, this delay is restricted to an interval shorter than the refractory period of the recipient atrium to prevent it from contracting a second time shortly after its spontaneous systole. Although the double pacemaker system allows for either donor or recipient sinus rhythm to dictate the rate of the other heart (Fig. 1 and 2), the donor heart beats faster under most circumstances because of the intrinsically faster sinus rate of the denervated donor heart, which usually beats at a rate of approximately 90 to 110 beats/min.[5] However, during emotion or exercise, transient acceleration of the recipient heart, which remains under autonomic control, will allow the recipient heart to control the rate of the donor heart.

Double atrial-triggered pacemaker systems: We considered alternative systems for achieving sequential contractions of the two hearts; however, these systems would not permit either heart to dictate the rate of the other. Sequential contractions of the two hearts could be achieved using an atrial-triggered pacemaker with a sensing electrode on the donor atrium and a pacing electrode on the recipient atrium. This system would have the advantage of not restricting the delay between donor and recipient atrial systole; however, it would require that the donor sinus rate always exceed the recipient sinus rate, which does not consistently occur. In the event of acceleration of the recipient sinus node, stimulation of the recipient atrium at a critical coupling interval could incur the risk of inducing atrial tachyarrhythmia in the recipient heart.

An atrial-triggered pacemaker with a sensing electrode on the donor atrium and a pacing electrode on the recipient ventricle would have the same disadvantage as the former system, with the additional loss of atrial transport in the recipient heart due to atrioventricular (A-V) dissociation. However, we plan to use such a system in the event that a patient's own heart is in atrial fibrillation at the time of operation, thereby precluding sequential stimulation of the recipient atria. At the time of operation, A-V block would be induced surgically in the recipient heart to prevent intermittent capture of the recipient ventricles by the fibrillating recipient atria.

Another system that we considered involved the use of an atrial-triggered pacemaker with a sensing electrode on the donor ventricle and a pacing electrode on the recipient ventricle. This system would have resulted in loss of atrial transport in both hearts, and surgically induced A-V block in the recipient heart would have been necessary to allow the donor heart to dictate the rate at all times.

Potential problems: Two potential problems could arise in the double pacemaker system described. If atrial fibrillation developed in one of the two hearts, the fibrillating heart would be expected to cause a fast chaotic rhythm in the opposite heart. However, the respective pacemaker refractory periods of 540 (360 + 180) and 400 msec, would prevent the atrial rate of the opposite heart from exceeding 150 beats/min at any time. However, it is more likely that the fibrillatory waves would be imperfectly sensed and that a much slower irregular rate would occur in the atrium of the nonfibrillating heart.

Another situation that has arisen is a fall in the sinus

rate of both hearts to a level below the standby rate of both pacemakers. Figure 3 shows an electrocardiogram in which the donor pacemaker fires fractionally before the recipient pacemaker, with both pacemakers functioning in the standby mode. The standby rate of the recipient pacemaker is fractionally faster than that of the donor pacemaker, and therefore the recipient pacemaker spike progressively approaches the preceding donor pacemaker spike. To prevent this phenomenon in future systems we plan to have a standby rate of 75 beats/min in the donor pacemaker and 60 beats/min in the recipient pacemaker. Whenever the rate of both hearts falls to a rate of less than 76 beats/min, this will result in pacing of the donor heart at a rate of 75/min, followed by the recipient heart at an interval of 180 msec.

In conclusion, our experiences with the first patient with a biventricular bypass heterotopic cardiac homograft to undergo pacing in the described manner have proved satisfactory, and the system appears to have fulfilled the purpose for which it was designed.

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Perplexities and Complexities Concerning the Myocardial Infarction Border Zone and Its Salvage*

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The recognition that pump failure complicating an acute myocardial infarction is the consequence of a critical cumulative loss of left ventricular myocardium has resulted in a major effort to define and reduce the extent of the acute muscle damage. Fundamental to this approach is the concept that in the initial period after an infarction, a zone of ischemic but viable myocardium exists whose survival can be influenced by a favorable alteration in the balance between energy supply and demand at this time.[1] This "border zone" has been the subject of considerable recent investigation, and an important article on its characterization by Hearse et al.[2] recently appeared in this Journal. In view of this intense interest, it would be useful to examine some of the major questions related to the border zone: (1) Is there in fact such a zone? (2) How much myocardium does it comprise? (3) How long does such a zone remain as such after an acute infarct? (4) Can interventions be brought to bear to salvage this zone and, if so, would they always be beneficial in an uncomplicated infarct?

Nature and Course of Border Zone

Experimentally, there is a considerable body of cell,[3] biochemical[2] and contractile[4,5] evidence to substantiate the presence of a border zone after an acute myocardial infarction both surrounding[2] and superficial[6] to the area of maximal ischemia although, as Hearse et al.,[2] point out, this concept is not universally accepted. It has been argued that this zone is actually a heterogeneous combination of normal and infarcted myocardium, thus implying that an "all or none" phenomenon applies to any given cell. However, there is good evidence that the basic mechanisms affecting the contractility of ischemic myocardium and causing irreversible damage are quite different. The altered contractility probably results from a disorder in the calcium cycle that, in turn, is related to acidosis in the ischemic area. Although the mechanism of irreversible damage to ischemic myocardium has not been precisely defined, it appears to be related to damage of mitochondrial and sarcolemmal membranes that, in turn, may be related to reduced adenosine triphosphate and labilization of lysosomal enzymes. In addition, ischemia results in a sequence of cell changes that cause a decrease in contraction literally within seconds[4] whereas irreversible damage occurs considerably later.[3] Studies in man also support the concept that diminished or absent regional contraction is consistent with viable myocardium[7] that has the potential to improve with a favorable change in the ratio of oxygen supply to demand.[8,9]

In the setting of acute myocardial infarction, perhaps the more relevant questions relate to the amount of myocardium included in the border zone and its course with respect to time. Definitive answers are not yet at hand and one expects that they will be difficult to obtain, particularly in the clinical setting. In man, the determinants of both the size and time course of a

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myocardial infarct and its border zone are complex and variable, depending on multiple factors such as (1) the coronary artery which is causally involved and the site within it of the obstructive lesion, that is, proximal or distal; (2) the rapidity of development and severity of the coronary occlusion resulting in the infarct, that is, partial or complete; (3) the subsequent dynamic pathology of the coronary arterial lesion, that is, whether it becomes occlusive, propagates and extends or, conversely, reopens or recanalizes; (4) the functional status of the other major coronary arteries as well as their anatomic pattern, particularly with regard to the areas of left ventricular myocardium supplied, that is, in inferior infarctions, the presence and degree of right or circumflex dominance and the relative balance between them and, in anterior infarcts, the relative dependence of the interventricular septum on the first septal perforator and the varying degree to which the lateral wall is supplied by one or more diagonal vessels originating from the left anterior descending coronary artery or by circumflex marginal branches; (5) the anatomic pattern and adequacy of the coronary collateral circulation; (6) the coronary perfusion pressure; (7) the coronary microcirculation; (8) the myocardial oxygen requirements, which, in turn, relate to a multiplicity of factors; and (9) the subsequent chronic spontaneous expansion or retraction of the original scar or necrotic tissue, or both. Thus, quantitating and defining the "natural history" of an infarct and border zone in man present extraordinarily difficult tasks for the investigator.

Efficacy of Interventions and Time Course of Infarction and Border Zone

Experimentally, several reports have indicated that the extent and severity of myocardial ischemic injury can be altered substantially by various interventions that can be initiated several hours after coronary occlusion. Hearse et al.,[2] using a series of variables, define the size of the border zone in dogs as 8 to 15 mm in width and calculate that a considerable volume of myocardium is thus involved when tissue samples are obtained for analysis 21 to 26 minutes after coronary occlusion. However, there is also a considerable amount of evidence, ranging from the studies of both Wiggers and Blumgart in the 1930's to more recent work,[10–12] that the time constraints required for effective preservation of ischemic myocardium may be stringent, ranging from minutes to a few hours after the onset of infarction depending in part on whether the occlusion is complete or partial.[13] Certainly, it is clear that the efficacy of any intervention designed to preserve the border zone is likely to be inversely proportional to the interval after the infarct and these temporal constraints need to be defined more clearly.

Clinically, experience suggests that the time course of an acute myocardial infarction and the border zone may be quite variable. Patients presenting at comparable intervals after the onset of symptoms may have new Q waves in the initial electrocardiogram or, conversely, exhibit no new abnormalities, which only evolve considerably later in the course of infarction. Similarly, it is not uncommon for a patient with an "acute" infarct to exhibit evidence of tissue damage in a slow stepwise fashion over a relatively protracted period. The situation becomes even more complex when one considers that the incidence of extension of an infarct (an event not always clinically obvious) may be greater than previously recognized.

Whether interventions can salvage the border zone or will benefit patients with an uncomplicated infarct is surprisingly difficult to answer because of the incomplete and conflicting nature of the relevant available information. Clearly, such interventions are a logical approach in patients with overt or impending cardiogenic shock. Wiggers originally conceptualized that in this setting a vicious cycle produced the deteriorating course of most patients, with a decreasing blood pressure due to loss of contractile myocardium producing increasing depression of cardiac function through its influence on coronary perfusion.[14] However, the pathophysiologic mechanisms operating in an uncomplicated myocardial infarction are not comparable with those of cardiogenic shock.

Transmural Versus Nontransmural Infarct

It is generally accepted that patients with a myocardial infarction severe enough to produce acute or chronic left ventricular dysfunction have a relatively unfavorable prognosis. However, there is also recent evidence[15] that patients with a small or nontransmural infarct have a long-term prognosis that is as poor or even worse than that of patients with a transmural infarct. Most patients with a nontransmural infarct have two or three vessel coronary disease,[15] and the new "small" infarct is frequently the forerunner of more serious complications and an unstable course in the early follow-up period. Such patients appear to be particularly prone to sudden death, which in one study[16] had an incidence over a 36 month follow-up period that was more than twice as great as that in patients with transmural infarction. It is thus possible that patients with a transmural infarct have subsequent scar formation with minimal if any residual ischemic tissue whereas patients with a nontransmural infarct, having larger zones of myocardium that are either chronically or potentially ischemic, may be more prone to recurrent severe ischemic events including electrical instability. However, a reduction in infarct size has been shown to diminish the incidence of ventricular arrhythmias.[17]

Patients with a nontransmural infarct and S-T segment depression (particularly in the anterior leads) also appear to have a relatively poor prognosis.[18] This finding is consistent with the results of the prospective outpatient study of the Coronary Drug Project in which it was observed that after hospital discharge for a documented myocardial infarction, a resting electrocardiogram characterized by S-T segment depression of the "ischemic" type was the most important independent risk predictor of all clinical and electrocardiographic findings studied.[19] In these *specific* circumstances, if one accepts the view that ischemia may be present, the extensiveness, location and subsequent rate of pro-

gression of coronary obstructions (with a resultant increase in ischemia) would be dominant prognostically in the posthospital phase of the disease process. Therapy would then logically focus upon either complete restoration of blood flow to the ischemic areas or at least prevention of further deprivation of already compromised flow.

Conclusions

In summary, it is clear that the study of the border zone, such as that by Hearse et al.,[2] and the feasibility of its salvage is a valid and indeed an important undertaking in patients who are at high risk for the development of acute pump failure and cardiogenic shock or chronic left ventricular dysfunction and heart failure. Additional studies are needed before one can assume that border zone salvage, if clinically feasible, is necessarily beneficial in the uncomplicated infarct. The relation between infarcted and ischemic areas and cardiac "electrical function" must be more fully assessed to determine whether interventions directed toward border zone salvage decrease or actually increase the incidence of lethal ventricular arrhythmias and sudden death. However, this area of concern should not become predominant in the use of resources that are urgently needed to develop better diagnostic methods having a higher degree of sensitivity and specificity as well as quantitative capabilities for use in both screening and longitudinal follow-up of patients as well as allowing recognition of those who are particularly prone to sudden death. Similarly, it should be remembered that the development of therapies to attenuate or stop progression, promote regression[20] or, ideally, prevent the atherosclerotic process will, in the final analysis, be the major determinant of whether a truly meaningful impact can be made on the still staggering mortality rate of this disease.

While awaiting the resolution of these important issues concerning the border zone, the clinician may, perhaps, be reassured that the current conventional treatment of patients with an uncomplicated myocardial infarction may be of value to the degree that relief of chest pain, bed rest, sedation, reassurance and management of arrhythmias all serve to decrease myocardial energy requirements and reduce ischemia.

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LETTERS TO THE EDITOR

PROPHYLACTIC PERMANENT PACING

Ritter et al.[1] concluded that patients with transient atrioventricular (A-V) block in association with right bundle branch block and left anterior hemiblock during acute myocardial infarction "should be given permanent pacing to prevent late sudden death." They added that "further randomized studies of pacing therapy on this group seem unjustified." We believe that this conclusion is premature and that the issue of prophylactic permanent pacing is still unsettled.

In 1974 we adopted a policy of implanting a permanent pacemaker in every patient with persistent partial bilateral bundle branch block after acute myocardial infarction. During that year, six such patients underwent pacemaker implantation, and the details of their follow-up are included in Table I.

Five of these patients died 6 weeks to 8 months after pacemaker implantation (mean 4 months) and only one patient is still alive (32 months after implantation). Three died in the hospital of congestive heart failure and two died suddenly outside the hospital. In the latter two patients the pacemaker was found to have been functioning properly shortly before death.

Recently, Ginks et al.[2] found that 10 of 14 survivors of acute myocardial infarction complicated by transient complete heart block but with partial bilateral bundle branch block, were alive and well 21 to 65 months later, without the aid of a pacemaker, and that long-term pacing failed to prevent sudden death in two patients. They concluded that long-term pacing is not justified in patients with partial bilateral bundle branch block persisting after complete heart block in acute myocardial infarction. Nimetz et al.[3] found that late mortality was not influenced by the presence or absence of transient A-V block in patients with partial bilateral bundle branch block complicating acute infarction.

Although some patients may well benefit from prophylactic pacing, many others would have an unaltered prognosis because the outcome is frequently determined by the patient's poor myocardial function. In such patients the prevention of advanced heart block does little to reduce mortality. And in some, permanent pacing might do more harm than good in light of the loss of atrial contribution, operative morbidity and unnecessary expense.

The contradictory published data, including our own results presented here, indicate that more data are needed before definite conclusions are made. In view of the small numbers of patients who survive acute myocardial infarction with partial bilateral bundle branch block, a randomized multicenter prospective study, already recommended by several authors,[3,4] seems highly desirable.

TABLE I (Amikam and Riss)

Follow-Up of Paced Patients Who Had Partial Bilateral Bundle Branch Block After Acute Myocardial Infarction

Case no.	Age (yr)	Site of Infarct	Conduction Defects	Transient 3° AVB	Follow-Up
1	58	Ant	CRBBB, LAHB, 1° AVB	No	Died of CHF after 6 wk
2	73	Ant, inf	CRBBB, LAHB, 1° AVB	No	Died of CHF after 7 mo of CHF
3	79	Ant	CLBBB, 1° AVB	Yes	Died of CHF after 6 wk
4	50	Ant	CRBBB, LAHB, 1° AVB	Yes	Died suddenly after 6 wk
5	66	Ant	CLBBB, 1° AVB	No	Died suddenly after 8 mo
6	60	Ant, inf	CRBBB, LAHB	Yes	Alive after 32 mo

Ant = anterior; AVB = atrioventricular block; CHF = congestive heart failure; CLBBB = complete left bundle branch block; CRBBB = complete right bundle branch block; Inf = inferior; LAHB = left anterior hemiblock.

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REPLY

We recommended permanent pacing only for a narrowly defined group, namely, patients with complete right bundle branch block plus left anterior hemiblock and third degree transient atrioventricular (A-V) block complicating an acute myocardial infarction. Only Patients 4 and 6 of Amikam and Riss belong to this group; Patient 4 died suddenly at 6 weeks and Patient 6 was alive at 32 months. We would not have implanted a pacemaker in Patients 1, 2 and 5 because they did not have third degree A-V block. We would have implanted a pacemaker in Patient 3 with complete left bundle branch block plus first degree A-V block although our data do not fully substantiate this procedure owing to an insufficient number of patients.

Ginks et al.[1] described 11 patients with complete right bundle branch block plus left anterior hemiblock plus third degree block without permanent pacing; 4 of 11 patients died, which is a better survival rate than observed in our series. Nimetz et al. (Ref 3 of Amikam and Riss) reported late deaths in 4 of 9 patients with complete right bundle branch block plus left anterior hemiblock plus transient third degree A-V block, but 2 of the survivors had permanent pacemakers; death occurred in 4 of 12 patients with complete right bundle branch block plus left anterior hemiblock without third degree block. If these data are added to our series and others using a 1 year follow-up time, the difference between pacing and not pacing is significant (Table I). Hence, it appears that survival is much better at 1 year with pacing than without pacing.

TABLE I (Atkins et al.)

One Year Follow-Up of Patients Who Had Third Degree A-V Block With Complete Right Bundle Branch Block Plus Left Anterior Hemiblock During Acute Myocardial Infarction

	Unpaced (no.)		Paced (no.)	
Ref	Patients	Deaths	Patients	Deaths
3	8	5	0	0
4	8	6	7	0
5	2	0	2	0
6,7	6	5	12	2
2	7	4	2	0
1	10	1	1	0
Amikam and Riss	0	0	2	1
Total	41	21(51%)	26	3(12%)

A-V = atrioventricular; Ref = reference number.

Because our study was retrospective and unrandomized, the conclusion is not as strong scientifically as we and others would like. However, our statement that further randomized studies of patients in the group seem unjustified was based not only on the clear-cut difference in long-term prognosis in our series but also took into account the difficulties of attempting to assemble a randomized series. A case load of 500 acute myocardial infarctions per year would be likely to produce 25 patients with right bundle branch block plus left anterior hemiblock. Eleven of these 25 patients would manifest transient third degree A-V block and, of the 11 with such block, 5 would die in the hospital of pump failure, leaving 6 patients per year for randomization. Hence, to randomize enough patients to have 30 in each group would require 10 years. We believed it unjustified to initiate a study to randomize when the odds of obtaining scientifically valid information in a reasonable period of time are nil and the principal reason for restraint is the expense of a pacemaker. A large multicenter trial to randomize patients may be justified because data on a substantial number of patients could be obtained in a reasonable amount of time and resolve this important problem.

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VECTORCARDIOGRAPHY AND BODY SURFACE ISOPOTENTIAL MAPPING TO DETECT OLD MYOCARDIAL INFARCTION

I enjoyed immensely the report by Vincent et al.[1] on the contribution of body surface isopotential mapping to the diagnosis of old inferior myocardial infarction. Techniques useful in this diagnosis are of great practical import because QS or QR acute patterns of inferior leads in the standard electrocardiogram are often replaced by nondiagnostic qR or rS patterns.

Vectorcardiography has also been found useful in detecting old inferior myocardial infarction in the absence of diagnostic Q waves in the inferior leads of the standard electrocardiogram. In addition, even inferior infarcts producing early inferiorly oriented forces and resulting in rS patterns in leads III and aVF have not escaped diagnosis by vectorcardiography.

If the authors have recorded vectorcardiograms in their patients, I would be interested in the characteristics of the QRS loops of the frontal plane, particularly in their patients exemplified by Figures 5 and 6, who did not display diagnostic features of inferior myocardial infarction in the 12 lead electrocardiogram.

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REPLY

Although we recorded vectorcardiograms in some of our patients, the sampling is incomplete and the information not suitable for formal analysis.

Vectorcardiography certainly seems to be superior to scalar electrocardiography in the diagnosis of previous inferior wall infarction. Sohi et al.[1] have reported that the body surface map is superior to the scalar electrocardiogram and vectorcardiogram in detecting patients with previous infarction or severe coronary artery disease. Further comparison of body surface map data with vectorcardiographic data is necessary to establish the role of each of these procedures in the diagnosis of previous infarction.

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SPECIFICITY AND SENSITIVITY OF TECHNETIUM-99M PYROPHOSPHATE MYOCARDIAL IMAGING IN ACUTE MYOCARDIAL INFARCTION

Berman et al.[1] claim enhanced specificity of technetium-99m pyrophosphate myocardial imaging in acute myocardial in-

farction by classifying as equivocal all scintigrams with a 2+ diffuse pattern. Their findings are of interest to us in view of our own data.[2,3]

Although a great majority of "false positive" technetium-99m pyrophosphate scintigrams may show a 2+ diffuse pattern, we have found higher levels of diffuse uptake in patients without clinical evidence of acute myocardial infarction[3] with scintigrams obtained on more than one occasion 2 hours after pyrophosphate injection. With their new classification, Berman et al. were able to enhance the specificity of the technetium-99m pyrophosphate technique by excluding 35 patients without evidence of acute myocardial infarction on the basis of a 2+ diffuse or equivocal pattern. However, 9 of their 18 patients (50 percent) with subendocardial infarction, 5 of 81 patients (6 percent) with transmural infarction and 1 patient with equivocal evidence of infarction had the same 2+ diffuse or equivocal scintigraphic pattern. Thus only enzymatic and electrocardiographic changes separated the patients with myocardial infarction from those without such necrosis. The significance of a 2+ diffuse pattern in patients with coronary artery disease without enzymatic or electrocardiographic changes of acute myocardial infarction cannot be assessed without histologic data and long-term follow-up studies. Although residual cardiac blood pool activity may explain some of these equivocal scintigrams, it is not clear how, in the absence of histopathologic data, one can exclude subclinical myocardial necrosis as a possible mechanism of the 2+ diffuse pattern.

By introducing the new equivocal category of positive technetium-99m pyrophosphate myocardial scintigrams, Berman et al. have tried to show increased specificity of this technique without giving the impression that its sensitivity is impaired. Whether the 2+ scintigram is classified as definitely positive or equivocal as Berman et al. suggest, one can improve upon the specificity of technetium-99m pyrophosphate imaging only at the cost of sensitivity and vice versa.

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REPLY

Our new classification system is designed to maximize specificity while only minimally decreasing sensitivity. By using an equivocal category for the 2+ diffuse scintigram, we were able to exclude from the positive category many patients without myocardial necrosis by enzymatic or electrocardiographic criteria. Although a few of these patients may have had islands of subclinical myocardial necrosis, undoubtedly the great majority, especially those whose cardiac catheterization studies with left ventriculography and coronary arteriography revealed no cardiac disease, were without necrosis and had residual cardiac blood pool activity accounting for their 2+ diffuse pattern. Therefore, the specificity of the positive scintigram for acute infarction is increased by the categorization. In addition, by separating the equivocal group from patients with definitely negative scintigrams, the implication of the definitely negative study regarding absence of acute infarction is enhanced. Ahmad's comments fail to consider the improved accuracy of both the positive and negative categories achieved by our new classification system, its major contribution. Necessarily, this markedly improved accuracy in definitely positive and definitely negative scintigraphy was achieved with modest loss of sensitivity. Thus, although most patients with 2+ diffuse uptake do not have necrosis, we do not not contend that all patients with such a pattern are never without myocardial necrosis. Indeed, when the 2+ pattern is seen, it is not possible to ascertain whether myocardial necrosis is or is not present. In this setting, the clinician must rely on the other standard methods for detecting myocardial necrosis. Importantly, myocardial technetium-99m scintigraphy may be performed serially or by computerized selective blood pool subtraction (Am J Cardiol, in press) to differentiate patients with 2+ diffuse activity due to acute necrosis from those with another cause of this pattern.

Finally, no test in clinical medicine has absolute sensitivity and specificity. Indeed, the electrocardiogram, undoubtedly over time the single most useful tool for detection of infarction, frequently demonstrates nonspecific ST-T wave abnormalities. When these abnormalities are present, the electrocardiographer cannot state with confidence whether subendocardial ischemia or necrosis is present or absent. But the electrocardiogram may have Q waves with high diagnostic specificity for acute infarction. Only the staunchest of cynics would state that because electrocardiography frequently reveals nonspecific ST-T wave changes, it is not useful in the assessment of acute myocardial infarction. Technetium-99m pyrophosphate scintigraphy is not a perfect test for the diagnosis of infarction. However, if one is aware of the meaning of certain nonspecific patterns, the implications of the definitely positive and definitely negative pyrophosphate scintigram make the study considerably more useful in the clinical detection of acute myocardial infarction.

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ABNORMAL P WAVE PATTERN IN REYE'S SYNDROME

Abnormal P wave patterns have been reported to occur as an electrocardiographic manifestation of focal disease of the central nervous system.[1–3] Our recent experience with a 12 year old patient with Reye's syndrome suggests (1) that such electrocardiographic findings may result from a nonfocal process in the central nervous system, and (2) that previous explanations for the electrocardiographic changes seen in Reye's syndrome deserve to be reevaluated.

Case summary: A 12 year old white girl was admitted to D.C. Children's Hospital because of the gradual onset over 18 to 24 hours of delirium associated with nausea and vomiting. Upon admission, she was noted to be grossly disoriented.

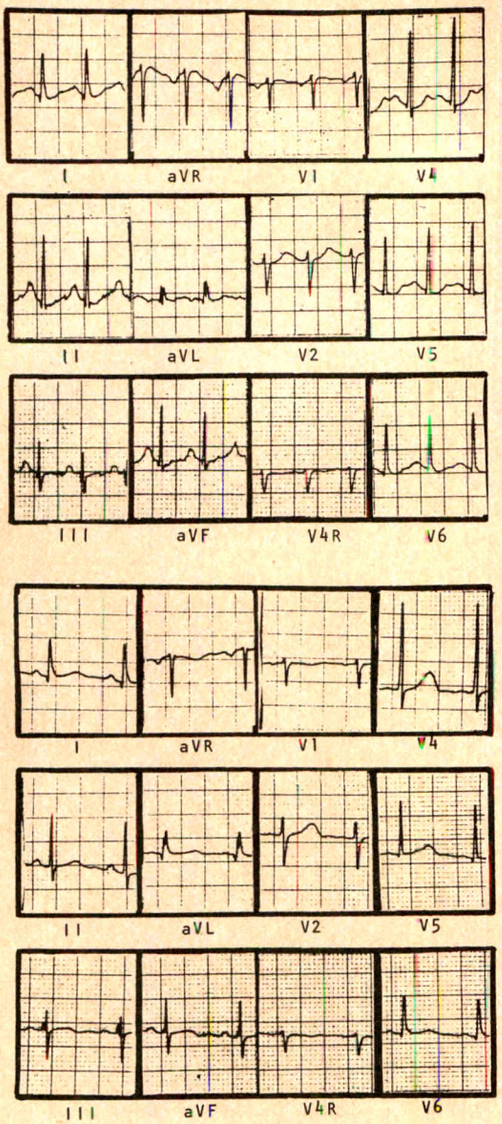

FIGURE 1. Electrocardiograms. **Top,** on admission. **Bottom,** 3 days after admission.

Neurologic examination revealed decorticate posturing without focal deficits. A serum ammonia level was 286. Serum electrolytes (Na, K, Cl, $CO_2^=$, Ca^{++}, $PO_4^=$) were normal. The patient was believed to have Reye's syndrome and a Richardson screw was inserted for monitoring intracranial pressure. An indwelling central venous pressure catheter was inserted to assist in fluid administration. The chest X-ray examination was normal. An electrocardiogram (Fig. 1A) revealed sinus tachycardia at a rate of 167/min. The P waves in lead II were 2.8 mm high and 3.0 mm wide. Nonspecific flattening and 0.4 mm depression of the S-T segment was present in leads I, II, aVL aVF and V_4 to V_6. Initial determination of intracranial pressure was 120 mm water, ultimately rising to a high level of 210 mm water. The central venous pressure consistently remained less than 7 mm water. After therapy with mannitol, neomycin and ventilatory support, the intracranial pressure returned to normal. The patient's condition improved and 3 days after admission, no neurologic residual impairment remained. A second electrocardiogram taken at this time (Fig. 1B) was normal.

The development of wide peaked P waves as well as nonspecific S-T segment abnormalities was observed in this patient only during an abbreviated period of central nervous system decompensation due to a generalized intracranial process. Previous reports[1,2] of such abnormalities of the P wave and S-T segment associated with the central nervous system have been limited almost exclusively to focal injuries, usually subarachnoid hemorrhage. Hammer et al.[3] reproduced transient S-T segment changes intraoperatively in a patient with subarachnoid hemorrhage by direct stimulation of the circle of Willis. Noting that this arterial system is richly innervated with autonomic nervous system endings, they proposed that such electrocardiographic changes were mediated by way of the autonomic nervous system. In support of this hypothesis are studies[4] in which the electrocardiographic changes have been reproduced or blocked with various pharmacologic interventions involving the autonomic nervous system.

Recent vectorcardiographic analyses[5] of abnormal P wave patterns in patients with central nervous system disease have demonstrated multiple notches in the vector loop of the peaked and prolonged P wave, consistent with conduction delay through the atrium. In our patient the absence of pressure-volume changes in the right atrium as evidenced by a constant and normal central venous pressure suggests that there was no anatomic basis for the production of the "right atrial strain." A more likely alternative is that the intraatrial conduction delay resulted from a change in autonomic nervous system tone.

Cardiac findings consisting primarily of electrocardiographic abnormalities are not uncommon in Reye's syndrome. A previous clinicopathologic study[6] of eight patients attempted to explain such changes on the basis of various degrees of microscopic fat deposition. A humoral process mediated by the central nervous system would seem to better fit the temporal sequence of changes such as those observed in our patient.

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STATISTICAL CONSIDERATIONS IN DETERMINATION OF VENTRICULAR VOLUME FROM ECHOCARDIOGRAPHIC AND ANGIOGRAPHIC DATA

Teichholz et al.[1] examined the relation of major (l) and minor (d) axes of the left ventricle in the absence of asynergy as de-

termined from 100 left ventriculograms. As their graph of the ratio of major to minor axis measurements (l/d) versus minor axis (d) was nonlinear, they rejected the commonly used assumption that the major axis is twice the minor axis for all persons. For estimating left ventricular volume, it is generally assumed that the left ventricle has the approximate shape of an ellipsoid of revolution, and thus $V = (\pi/6)d^2l$. Though d can be estimated routinely by ultrasound, l cannot. The authors show that by using their hyperbolic equation to estimate l from the d determined by ultrasound, they obtain more accurate predictions of V in synergic hearts than is obtained by using $l = 2d$ in the volume calculation.

We contend that the authors have misinterpreted their data because of a lack of appreciation of the statistical "regression toward the mean" phenomenon. We show that they have not disproved any assumption about left ventricular geometry; indeed, the hyperbolic equation derived can be expected to be of value in the estimation of left ventricular volume based upon purely statistical considerations, even if the true length of the major axis is twice that of the minor axis.

Results: The measurements l and d are the sum of the true values for the patient (L and D), plus measurement errors (E_L and E_D). We shall assume that the true sizes have the relation $L = 2D$ for each patient, and shall show that the results of Teichholz et al. are consistent with this assumption. If the true sizes (L, D) and the errors (E_L, E_D) follow Gaussian distributions, then it is a standard statistical result[2] that the expected value of l for a given measured value of d is expressed as

$$E[l|d] = \frac{cov}{\sigma_1^2} \cdot d + \mu_1 \left(2 - \frac{cov}{\sigma_1^2}\right), \qquad (1)$$

where cov denotes the covariance between d and l, and μ_1 and σ_1^2 denote the mean variance of d. Thus, the expected value of l/d for a given measured value of d is given by

$$E[(l/d)|d] = \frac{cov}{\sigma_1^2} + \mu_1 \left(2 - \frac{cov}{\sigma_1^2}\right)/d, \qquad (2)$$

which describes a hyperbolic curve. Therefore, the hyperbolic relation between (l/d) and d results even when it is assumed that the true sizes of the major and minor diameters are related by $L = 2D$. When d is estimated as $4a/\pi l$ from cineangiograms as described by Teichholz et al., it is easy to show that approximately $cov/\sigma_1^2 = 2(\omega^2 - \zeta^2)/(\omega^2 + \zeta^2)$, where ω^2 denotes the variance in the true D among individuals, and ζ^2 denotes the measurement variance in d for a given individual. Thus, expression (2) becomes

$$E[(l/d)|d] = \frac{2(\omega^2 - \zeta^2)}{(\omega^2 + \zeta^2)} + \frac{4\mu_1\zeta^2}{d(\omega^2 + \zeta^2)}. \qquad (3)$$

If there is no measurement error ($\zeta^2 = 0$), then expression (3) equals the constant 2. That is, in the absence of measurement error, the expected value of l/d for a given observed d equals 2. With measurement error, however, the regression toward the mean phenomenon implies that a hyperbola results, even though $L = 2D$ for each patient.

To lend support to the validity of their hyperbolic relation between l and d over the usual $l = 2d$, Teichholz et al. use their graph of l/d versus d to predict l for a given echocardiographically observed d and solve for ventricular volume. Let us denote the authors' function by $E[l/d]$. For an individual with major and minor axes of lengths L and D, we will assume with the authors that the left ventricular volume is given by $V = \pi D^2 L/6$. With $\hat{d}$ denoting the estimate of the minor axis determined echocardiographically, Teichholz et al. show that

$$V_1 = \pi\hat{d}^2 E[l/\hat{d}]/6$$

is a better estimate of true V than is $V_2 = \pi\hat{d}^2(2\hat{d})/6$ for patients without left ventricular asynergy. Rather than disprove $L = 2D$, however, this result can be explained on purely statistical grounds even when $L = 2D$. If $\hat{d}$ is an unbiased estimator of D, then it is easily shown that both V_1 and V_2 are biased estimators of the true V. The expected bias in V_2 over a population of individuals equals $\pi\gamma^2\mu_1$ where γ^2 denotes the variance in the echocardiographic measurement error in $\hat{d}$. The expected bias of V_1 equals $(-\pi\zeta^2\mu_1/3)$. Because the variance (γ^2) in the echocardiographic measurement error of $\hat{d}$ can be expected to be at least as large as the variance (ζ^2) in the angiographic measurement error of d, the magnitude of the expected bias of V_2 is at least three times that of V_1, assuming that $L = 2D$ is a true relation.

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References

1. **Teichholz LE, Kreylen T, Herman, MV, et al:** Problems in echocardiographic volume determinations: echocardiographic-angiographic correlation in the presence or absence of asynergy. Am J Cardiol 37:7–11, 1976
2. **Rao CR:** Linear Statistical Inference and Its Applications, second edition. New York, John Wiley, 1965, p 202

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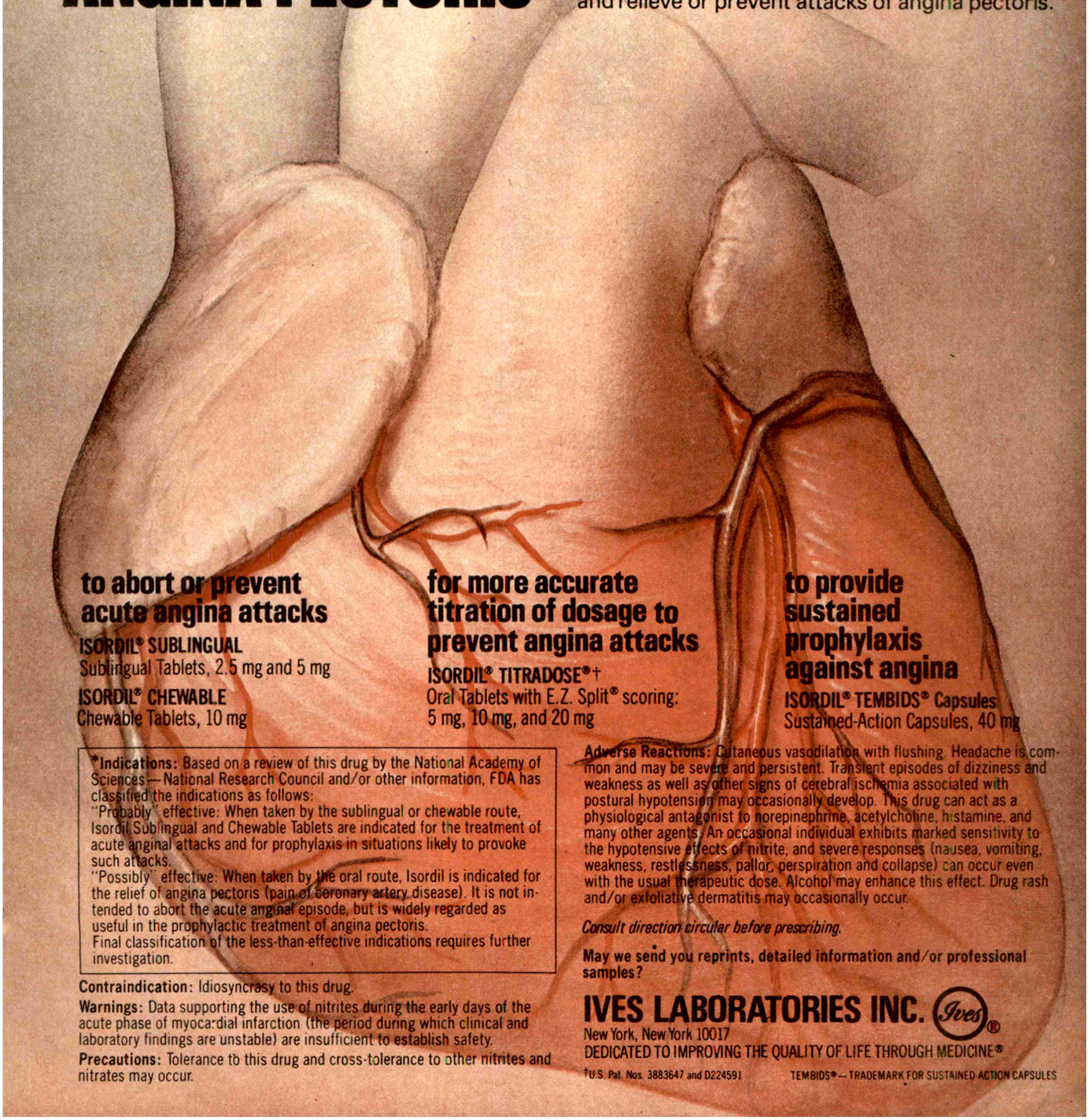

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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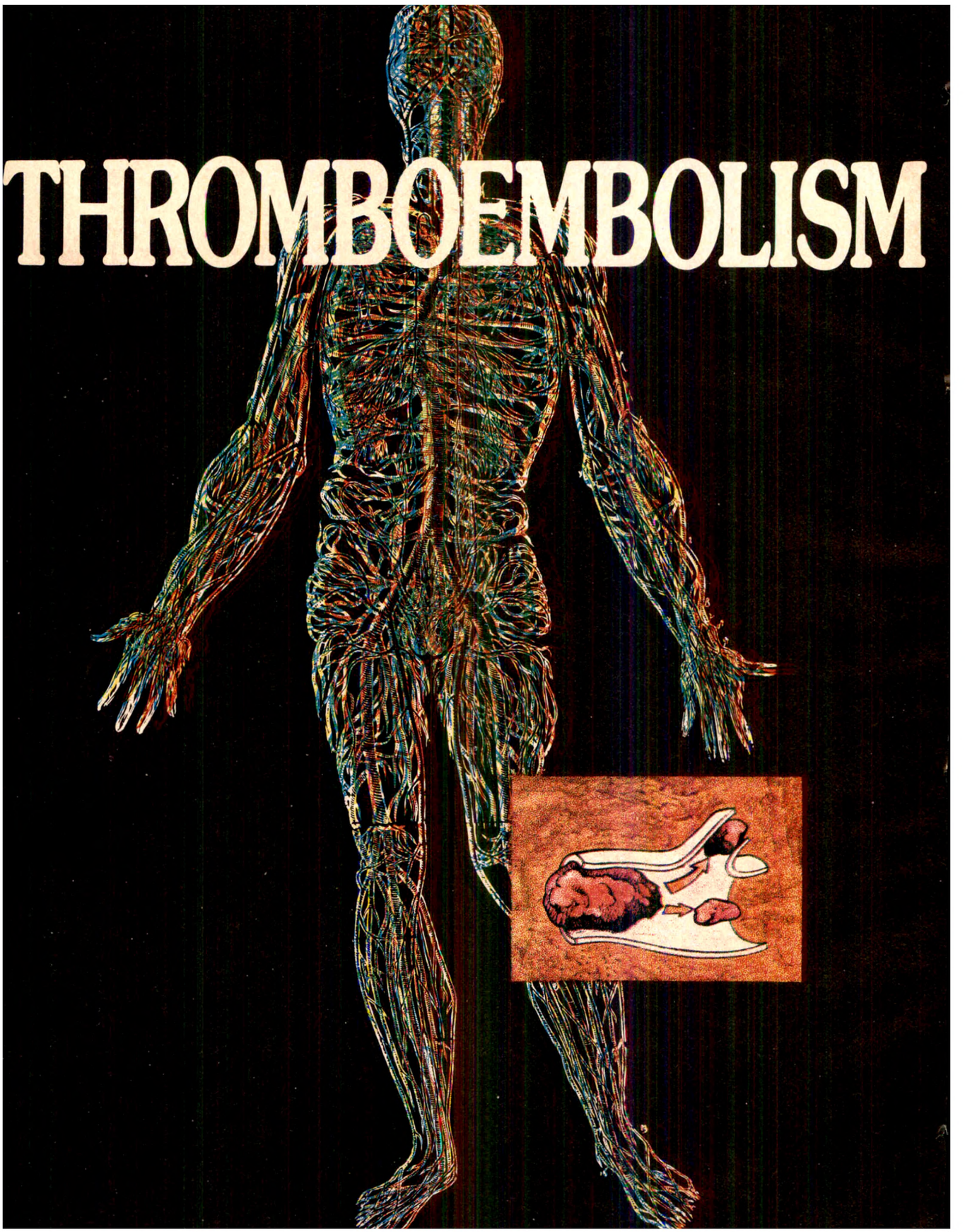

COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

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Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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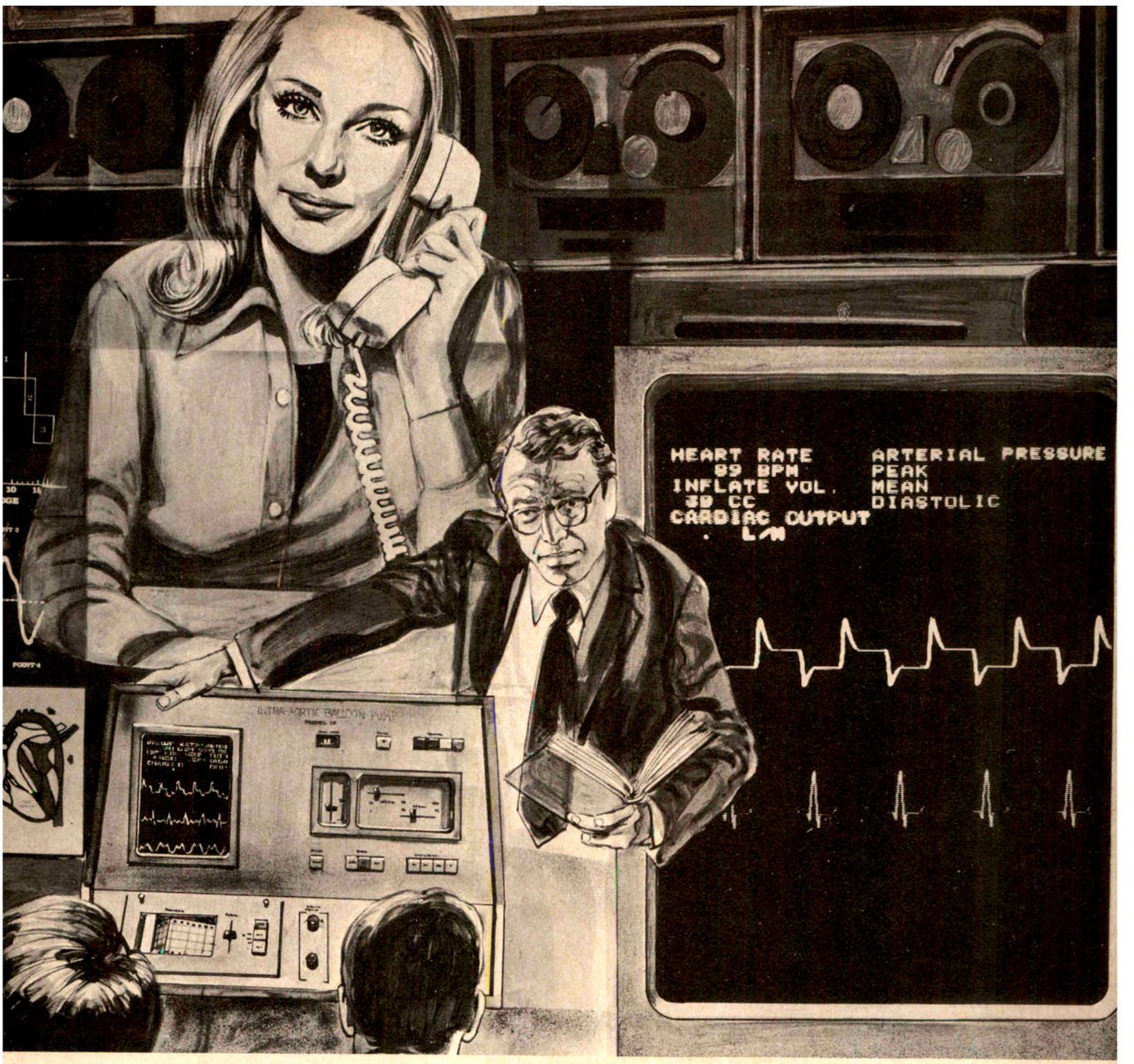

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ACTION: Nitroglycerin is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effect.
INDICATIONS: Prevention and treatment of angina pectoris.
PRECAUTIONS: Headache is a sign of overdosage, so reduce dosage. Occasionally elderly patients may develop postural hypotension with faintness upon suddenly arising. May be contraindicated in patients with marked anemia, increased intraocular pressure or increased intracranial pressure. Don't use in patients with a known idiosyncrasy to nitrites.
DOSAGE AND ADMINISTRATION: Usual dose is 1-2 inches, as squeezed from tube. Some patients require 4-5 inches. To determine optimal dosage, start with 1 inch, increase dose 1/2 inch at a time until headache occurs, then drop back to largest dose which doesn't cause headache. Apply to desired skin area with Dose Measuring Applicator. DO NOT USE FINGERS. Spread in thin, uniform layer. May be applied every 3-4 hours if necessary. Effective in control of angina pectoris, regardless of skin site of application, although patients may prefer chest site because anginal pain originates in this area. To stop treatment of anginal patients, gradually reduce dosage and frequency of application over period of 4-6 weeks to prevent characteristic nitroglycerin withdrawal reactions.
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REFERENCES: 1. Davidov ME, Mroczek WJ: The effect of nitroglycerin ointment on the exercise capacity in patients with angina pectoris.

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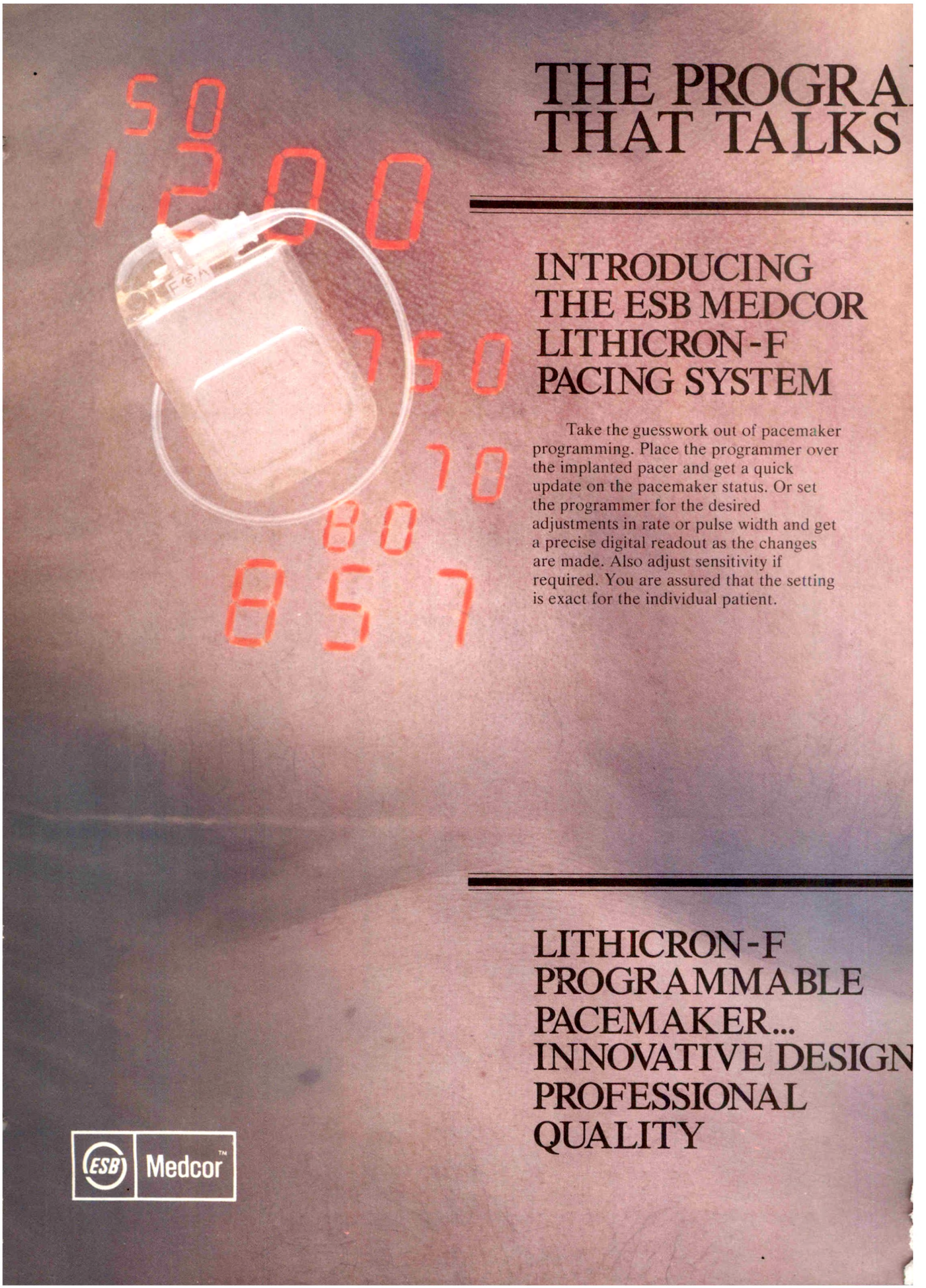

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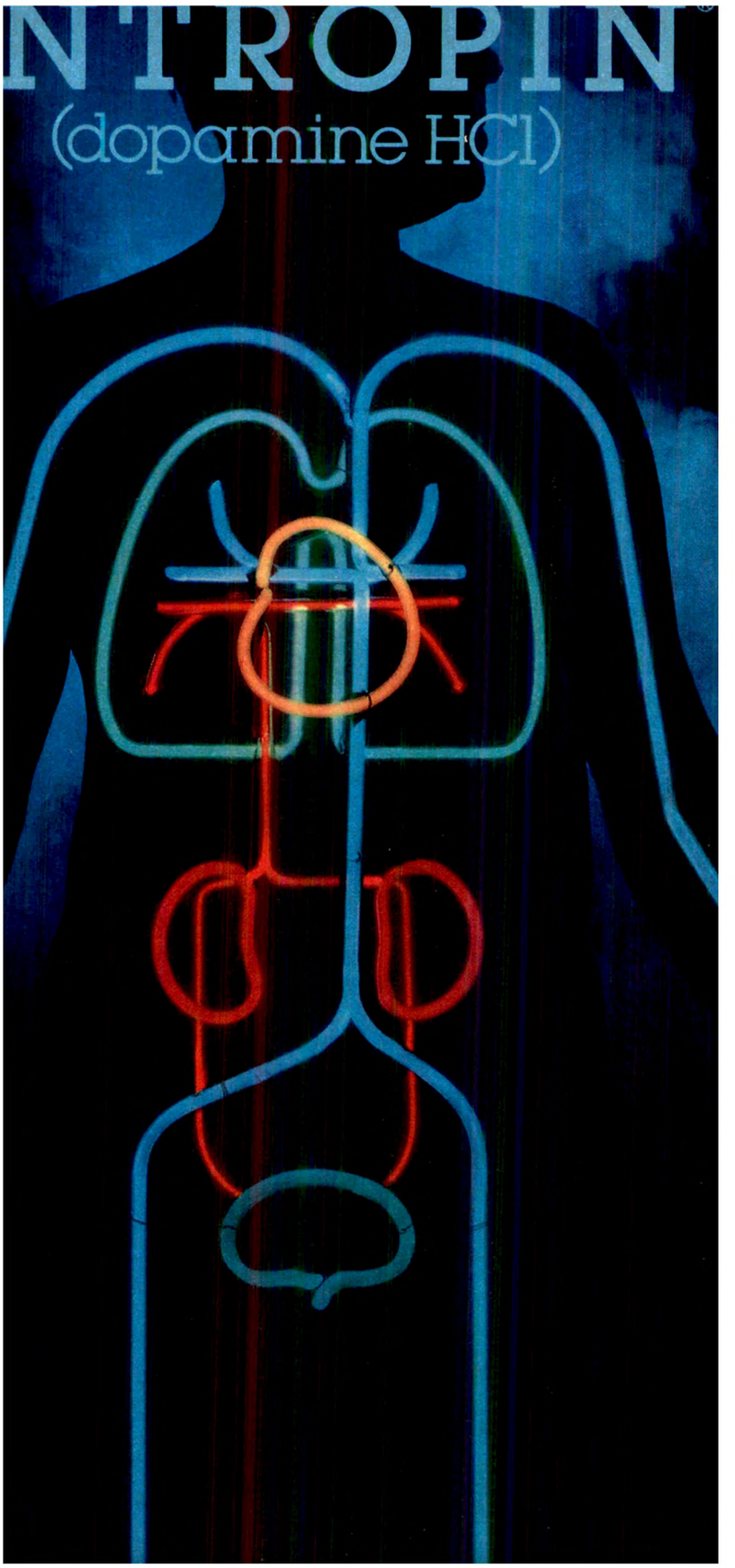
NTROPIN
(dopamine HCl)

In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

Maintains kidney function

The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
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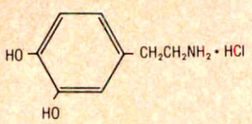
INTROPIN® (dopamine HCl)

(See last page of this advertisement for full prescribing information.)

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystaline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized..

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

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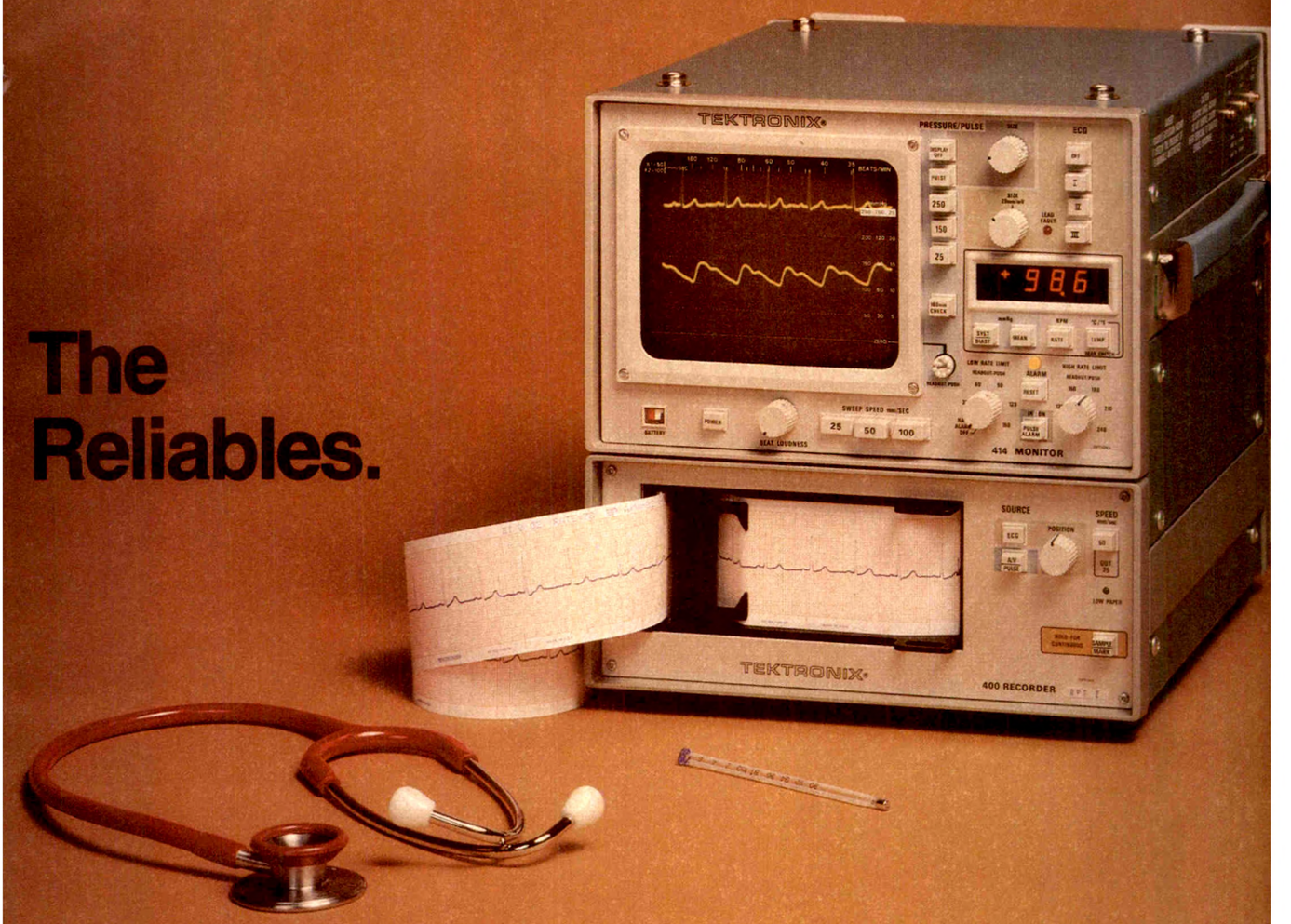

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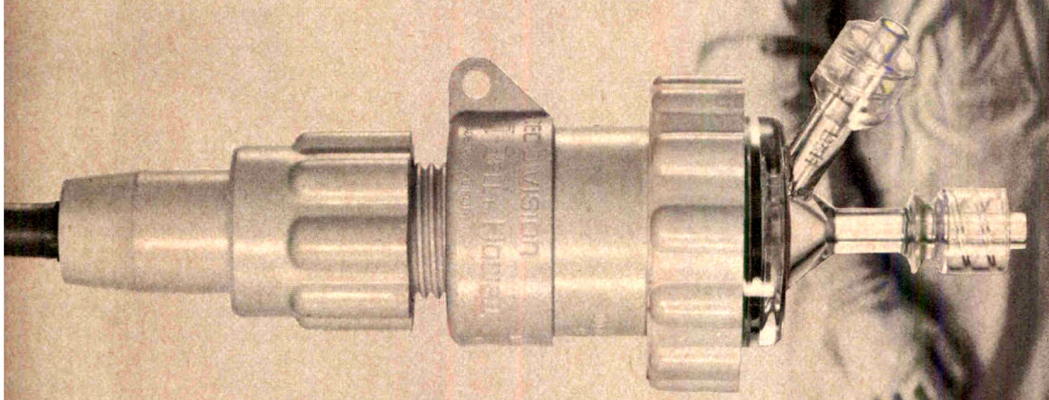

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Non-Steroidal 'Dyrenium' Helps the Patient Retain Essential Potassium Stores.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism, to increase diuresis in patients resistant to other diuretics. Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy when edema is due to pathological causes (see Warnings).

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing. 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

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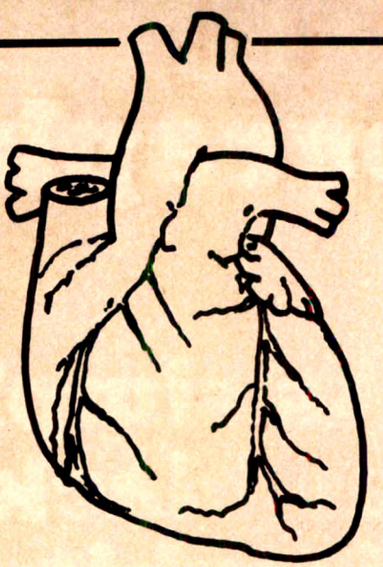

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A New Book! **PROGRESS IN CARDIOLOGY. 6.** Edited by PAUL N. YU, M.D., University of Rochester School of Medicine and Dentistry, Rochester, New York; and JOHN F. GOODWIN, M.D., Royal Postgraduate Medical School, London, England. (31 Contributors). In this sixth volume of a popular series, many European and American cardiologists and cardiac surgeons examine all major aspects of coronary revascularization—from surgical techniques in coronary artery bypass grafts to sophisticated hemodynamic and angiographic evaluation of the left ventricular function before and after coronary revascularization. Much of the material, particularly in regard to the clinical trials, has not previously been published. *211 pp. (7 X 10), illus., 1977, $15.00.*

A New Book! **MECHANICAL CONCEPTS IN CARDIOVASCULAR AND PULMONARY PHYSIOLOGY.** By JERRY FRANKLIN GREEN, Ph.D., University of California School of Medicine, Davis. This succinct, well-written text develops within the same conceptual framework the mechanics of both the blood vessels and pulmonary airways. Conceptual schemas developed are based upon unifying mechanical concepts. *166 pp. (5¼ X 7¾), illus., paperback, 1977, $10.00.*

ECHOCARDIOGRAPHY, 2nd ed. By HARVEY FEIGENBAUM, M.D., Indiana University School of Medicine, Indianapolis. Echocardiography, a relatively new technique that has become a major diagnostic tool in clinical cardiology, is described in this book. It contains the most recent developments and some previously unpublished, original material. Not only are the advantages of this technique described but also its limitations, pitfalls, and points of confusion. *512 pp. (7 X 10), illus., 1976, $19.50.*

A New Book! **CORONARY ARTERY SURGERY.** By JOHN L. OCHSNER, M.D., and NOEL L. MILLS, M.D., both of the Ochsner Clinic, New Orleans, Louisiana. This authoritative book encompasses many aspects of coronary artery disease. An abundance of precise, clinical information concerning use of the saphenous vein and the internal mammary artery as grafts, cannulation and extracorporeal circulation, type of operation and site of distal anastomosis, exposure of the heart, methods of vascular anastomoses, and management of complications is presented. Original drawings profusely illustrate these technical maneuvers. Anesthetic management and postoperative care are carefully outlined in a clear, step-by-step method. *About 250 pp. (7 X 10), illus., 1978, Ready Now.*

A New Book! **PEDIATRIC ECHOCARDIOGRAPHY.** By RICHARD A. MEYER, M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio. With chapters by RUSSEL L. UPHOFF, B.S. With the assistance of JOAN KORFHAGEN, R.D.M.S. This book provides the echocardiographer with an in-depth approach to the evaluation of both congenital and acquired cardiac disease in patients from the newborn period to adulthood. The approach is based upon thorough knowledge of both normal and pathologic anatomy and physiology of the heart. Individual cardiac defects have been grouped according to the hemodynamic effects produced by the lesions. *303 pp., illus., 1977, $17.00.*

A New Book! **CHEST PAIN: An Integrated Diagnostic Approach.** Edited by DONALD L. LEVENE, M.D. With RONALD F. BILLINGS, M.D., GEOFFREY M. DAVIES, M.D., JOHN EDMEADS, M.D., and FREDRIC G. SAIBIL, M.D. All of the University of Toronto Clinic, Sunnybrook Medical Centre, Toronto, Ontario, Canada. (8 Contributors). This highly practical and innovative book depicts an integrated diagnostic approach to one of the most common presenting symptoms in medicine. Clinically oriented, it brings together the numerous causes of chest pain, presents them by region, by system, and in order of frequency of occurrence, and explains how to separate the various entities. *203 pp., paperback, 41 illus., 1977, $11.00.*

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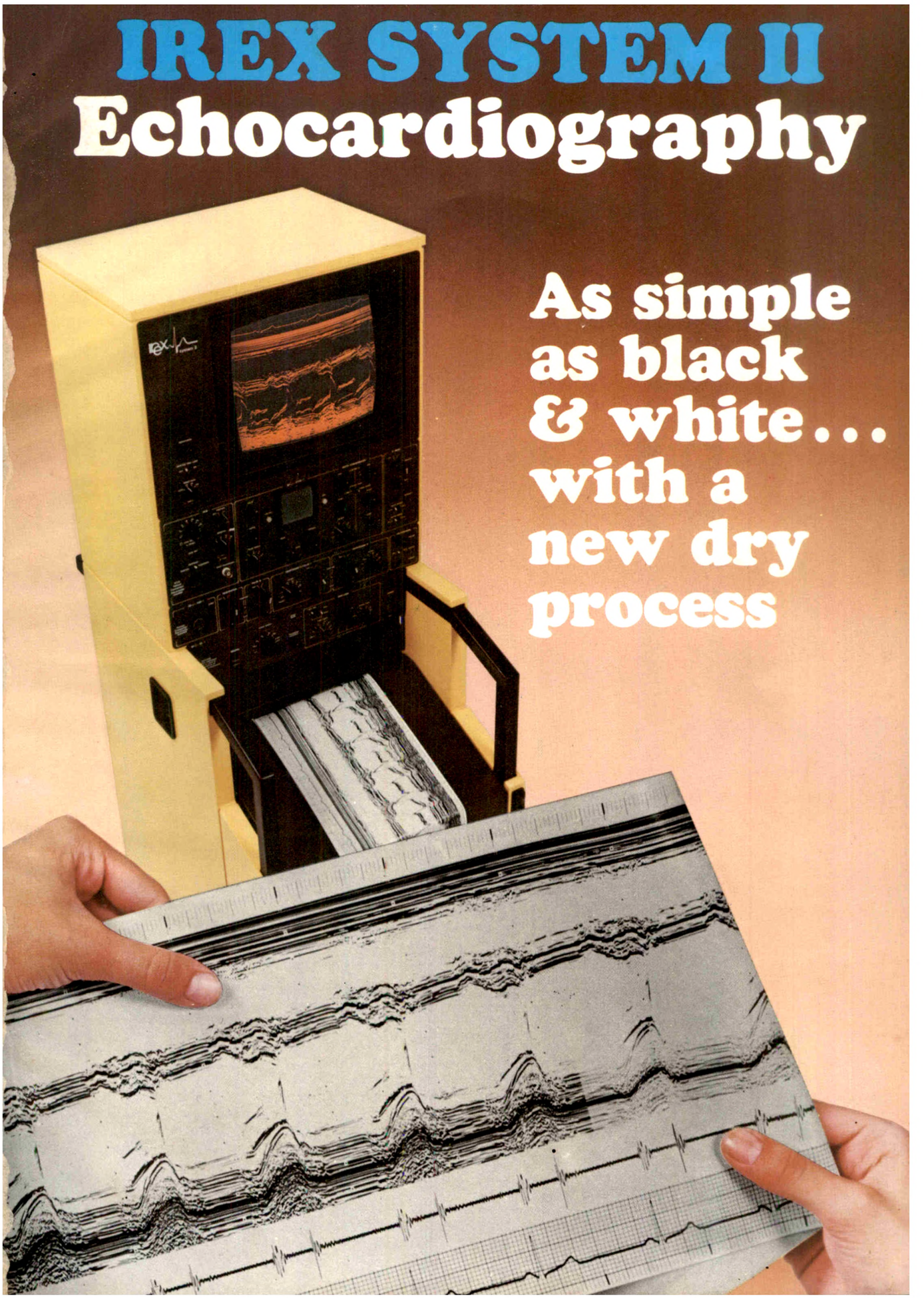

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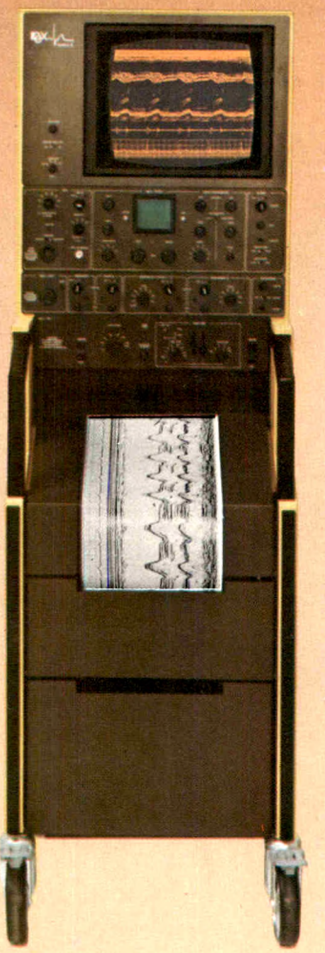

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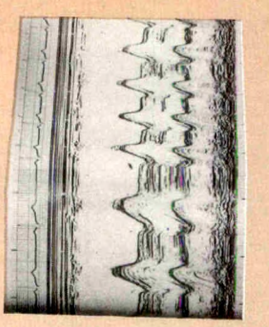

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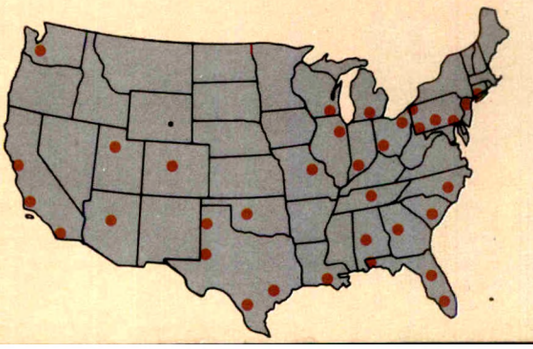

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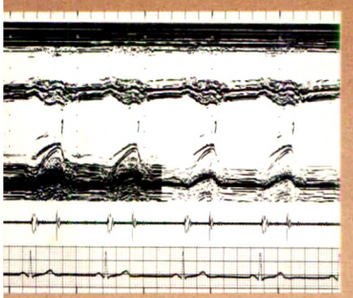

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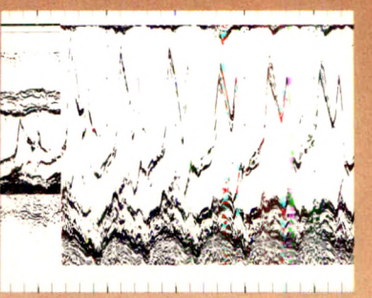

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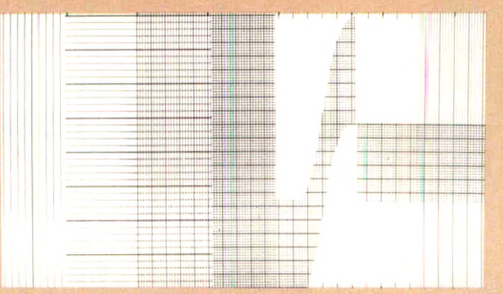

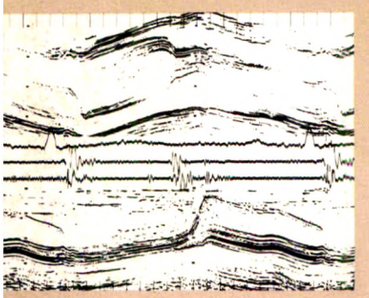

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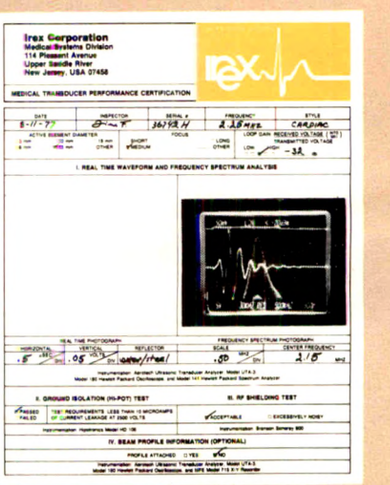

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Abstracts of Papers to be Presented at the 27th Annual Scientific Session of the American College of Cardiology Anaheim, California, March 6 to 9, 1978

In recognition of the enormous quantity of clinically relevant research regarding cardiovascular disease being performed throughout the world, the Scientific Program Committee for the 27th Annual Scientific Session of the American College of Cardiology expanded by nearly one-third the number of abstracts accepted for presentation in this year's program. Nevertheless, because a record number of 1,480 abstracts were submitted for evaluation this year, the 375 papers included in the program represent only 25 percent of those evaluated.

The generally high quality of all abstracts submitted for consideration made selection of the papers to be presented even more difficult than for previous Scientific Sessions. This year the total number of categories to which abstracts could be assigned was enlarged to 16. Each abstract was submitted to one of these categories and then reviewed by a panel of 10 nationally recognized authorities in that area. Thereafter, abstracts were accepted in order of highest grades in each category in proportion to the percent of the total number of abstracts in that category. Accepted abstracts were then grouped as closely as possible into areas of similar interest for presentation in the final program.

Although no method of abstract selection can be expected to be perfect, we believe that the objective process of peer review applied in the assessment of submitted research this year has resulted in a program of excellent diversity and the highest scientific caliber. We anticipate that as investigation regarding cardiovascular medicine continues to proliferate, the presentation of new data will constitute an increasingly important part of the Annual Scientific Sessions of the American College of Cardiology. In this way, the College will continue to foster its major role in the dissemination of both new and established principles regarding the cardiovascular system in health and disease.

Anthony N. DeMaria, MD, FACC
Chairman, Scientific Program Committee
27th Annual Scientific Session

Nemat O. Borhani, MD, FACC
Co-Chairman, Scientific Program Committee
27th Annual Scientific Session

MONDAY, MARCH 6, 1978
PM
PEDIATRIC ECHOCARDIOGRAPHY
3:30 to 5:30

EXPERIENCE WITH REAL-TIME TWO-DIMENSIONAL SECTOR ANGIOGRAPHY

Abdul J. Tajik, MD, FACC; James B. Seward, MD; Donald J. Hagler, MD, FACC; Douglas D. Mair, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minn.

By the use of an 80° phased array sector scanner, contrast studies were obtained during cardiac catheterization (CC) in more than 200 patients with various congenital heart diseases. Contrast material (1 ml of indocyanine green plus 5-10 ml of normal saline) was manually injected through the catheter. Sites of injection were determined by the clinical indication for CC, but usually they included caval and various intracardiac chambers. The sector angiograms thus produced were consistently of good quality and resulted in dense opacification of the injected chambers for 3-5 cardiac cycles. Hence, sector angiography (SA) not only allowed identification of anatomic relationships (as visualized from parasternal, suprasternal, apical, and subxiphoid transducer positions) but also allowed clear visualization of intracardiac left-to-right and right-to-left shunts, which could readily be localized to atrial or ventricular level. Accordingly, this technique was used reliably in excluding intracardiac shunts. SA also was useful in detection and quantitation of valvular regurgitation with results comparable to angiography. The advantages of SA include (1) no adverse effect of multiple injections on hemodynamics or patient, (2) ability to view the heart in multiple projections, (3) no interference from overlapping cardiac structures, (4) avoidance of dysrhythmia during injections, (5) avoidance of ionizing radiation, and (6) reduction in total amount of angiographic contrast agent needed. Our experience to date suggests that, during CC in selected situations, SA can readily and reliably be substituted for standard angiography.

EVALUATION OF ENDOCARDIAL CUSHION DEFECTS BY PHASED ARRAY SECTOR SCANNER.

David J. Fisher, M.D., Norman H. Silverman, M.D. FACC, Nelson B. Schiller, M.D. FACC and Patricia A. Hart, RDMS, University of California San Francisco.

Using an 80 degree two-dimensional scanner (2DSS) we examined 25 patients with various forms of endocardial cushion defects (ECD) confirmed by cardiac catheterization and in 13 of these by surgery. Using the apical (four chamber) view we defined the contribution of the anterior endocardial cushion to the atrioventricular valve leaflets. In complete ECD the anterior leaflet appeared either as a continuous echo across both ventricles when it was undivided (Rastelli Type 1C); or as separate "mitral" and "tricuspid" components when the anterior leaflet was divided and attached to the ventricular septum (Rastelli Type 1A). In addition the apical view defined the presence and size of a ventricular and atrial components of the ECD. Associated anomalies such as partial anomalous pulmonary venous drainage and aneurysmal pouches of the tricuspid valve can be detected. The relative sizes of the cardiac chambers can also be assessed. Long axis views demonstrated the ventricular septal defect (VSD). By sweeping from the left to right ventricle the atrioventricular valve was noted to be continuous across the VSD in complete (ECD). In the short axis of the heart at the level of the ventricles the presence of mitral valve clefts and paradoxical septal motion could be identified. Postoperatively the patch material used to close the septal defect was identified in 5 patients. Thus 2DSS yields precise noninvasive information in patients with various forms of ECD.

SUBXIPHOID REAL-TIME CROSS-SECTIONAL ECHOCARDIOGRAPHY FOR IMAGING THE RIGHT VENTRICLE (RV) AND RIGHT VENTRICULAR OUTFLOW TRACT (RVOT) David J. Sahn, MD, FACC; Ruthanne G. Sobol; Hugh D. Allen, MD, FACC; Dept. of Ped., U. of Az., Tucson, Az.

The RV body and the proximal portions of the RVOT close to the chest wall have been poorly imaged by echocardiography. Accordingly, the purpose of this study was to develop and validate imaging of the RV body and RVOT using a subxiphoid cross-sectional echocardiographic technique in 59 infants and children (age 1 day-15 yrs; 40 with anatomically normal RVOT's and 19 with forms of RVOT obstruction (RVOTO)). With a 30° mechanical sector scanner under the xiphoid notch aimed superiorly and sweeping a coronal plane parallel to a line between the patient's shoulders, images of the RV and left ventricle (LV) equivalent to those on anterior-posterior plane angiograms were obtained. Verification of structure identification was obtained in 4 patients using saline echo contrast injections. Of 19 patients later shown at cardiac catheterization to have RVOTO, 6 had valvar and infundibular (2 muscle bundles) RVOTO correctly predicted on echo. Infundibular disease alone was predicted in 2. In 4, the echo correctly suggested isolated valvar disease. In 1 infant, a short segment pulmonary atresia was correctly predicted and in 2 a small RV outflow chamber distal to an atretic tricuspid valve was imaged. Pulmonary artery (PA) bands were well visualized in 2 patients and origin of the PA directly from a truncus arteriosus was imaged in 2. Angiographic-echo correlation for the inner diameter of the main PA (17 patients) at the valve level was excellent (R= 0.93). This new technique provides imaging of the RV body and RVOT and permits noninvasive assessment of PA size and the sites of RVOT obstruction. With little patient discomfort, this technique produced better images of the RV body, RVOT and PA than echoes obtained from the chest wall.

SUBXIPHOID TWO DIMENSIONAL IMAGING OF THE ATRIAL SEPTUM Frederick Z. Bierman, MD; Roberta G. Williams, MD, Children's Hospital Medical Center, Boston, Mass.

The interatrial septum(IAS)was successfully imaged by subxiphoid two dimensional echocardiography in 19 patients, aged 1 day to 6 years whose diagnoses were established by catheterization, surgery, or postmortem exam. This group included: 3 patients with atrial septostomy by Rashkind technique, 4 with secundum type IAS defect and associated complex anomalies, 2 with sinus venosus defect, 5 with endocardial cushion defect, and 5 with stretched septum primum and patent foramen ovale(PFO). The septum was displayed in its anterior-posterior plane and scanned from the base to cephalad. Secundum defects including Rashkind septostomies appeared in the mid portion of the IAS and was occasionally associated with bulging of the septum primum into the right atrium. In 1 patient, pre and post Rashkind septostomy recording demonstrated enlargement of the IAS defect and flail septum primum. Two defects located in a postero-cephalad portion of the IAS were confirmed at surgery to be sinus venosus defects. Septum primum defects were located at the base of IAS and in patients with complete atrioventricular canal, it formed a confluence with the ventricular septal defect. An IAS defect could not be demonstrated in the 5 patients with PFO, but septum primum was found to bulge in the direction of the atrial shunt, and in 1 patient, patency was demonstrated by catheter passage and contrast injection. In summary, subxiphoid two dimensional echocardiography offers direct detailed imaging of the atrial septum in simple and complex lesions in the newborn and young child.

STRADDLING ATRIOVENTRICULAR VALVE: DIAGNOSTIC TWO-DIMENSIONAL ECHOGRAPHIC FEATURES James B. Seward, MD; Abdul J. Tajik, MD, FACC; Donald J. Hagler, MD, FACC; Douglas D. Mair, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minn.

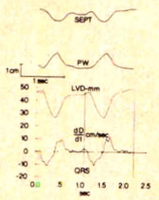
Straddling atrioventricular valve (S-AVV), a rare entity, is a diagnostic and management problem to the clinician and surgeon. Although M-mode echo and standard biplane angiography (BA) are useful in diagnosis, neither can accurately define AVV attachments. We describe our experience utilizing real-time 80° phased array sector echocardiography (SE) and sector angiography (SA) in the recognition of diagnostic features of S-AVV. We studied 6 patients (pts) with S-AVV (1 rt and 5 lt). All 6 had BA, and 4 had surgical confirmation. SE was performed at cardiac catheterization. Indocyanine green was utilized to obtain SA. An apical transducer orientation permitted simultaneous visualization of ventricular septum (VS), 2 ventricles, S-AVV, atria, and atrial septum. Visualized abnormal attachments of the S-AVV permitted distinction of 2 subgroups: (1) complete straddler (4 pts), insertions of the S-AVV into the body of both right (RV) and left (LV) ventricles, and (2) partial straddler (2 pts), insertions of chordae near crest or far side of the VS. Utilizing a selective atrial injection, both BA and SA demonstrated the same flow pattern in each subgroup (i.e., in early diastole, the bolus of dye passed through the S-AVV orifice, filling RV and LV simultaneously). The advantages of SE included (1) ease of recognizing and visualizing abnormal attachments of S-AVV, and (2) ability to recognize 2 subgroups of S-AVV. Since corrective surgery without sacrificing the S-AVV is feasible only in partial straddlers (recognizable only by SE), our experience indicates that SE should play an important role in the proper selection of patients for corrective surgery of this rare congenital heart defect.

ECHO LEFT ATRIAL/AORTIC ROOT RATIO IN VENTRICULAR SEPTAL DEFECT (VSD) L. Lester, MD; D. Vitullo, MD; P. Sodt; N. Hutcheon; O. Thilenius, MD, FACC; R.A. Arcilla, MD, FACC, University of Chicago, Chicago, Ill.

Echo-derived left atrial (LA) and aortic (Ao) dimensions, and LA/Ao ratios of 71 children with VSD were correlated with Qp/Qs ratios obtained by catheterization within 24 hours. Qp/Qs in group A (n=32) was <1.5,in B (n=22) 1.5-2.5, and in C (n=17) >2.5. Mean LA/Ao in A was 1.17 ± .028 SEM, in B 1.45 ± .055, and in C 1.57 ± .055. A differed from B ($p<0.001$) but B did not differ from C. Qp/Qs versus LA/Ao showed r=0.64 with wide distribution. Qp/Qs versus LA echo dimension (as % predicted normal [% PN] based on 96 normals) showed poor correlation (r=0.47). Lateral angiograms in end-systole were analyzed for LA and Ao dimensions at aortic root level, at 0° position (perpendicular to frontal plane) and at 5°, 10°, 15° and 20° angles below 0° using aortic root center as point of intersection. Angio LA dimension and LA/Ao declined progressively with increasing angulation whereas Ao remained relatively constant. Angio LA/Ao at each of the 5 planes correlated poorly with Qp/Qs (r range=0.15 to 0.39). The LA/Ao ratio has been utilized to estimate shunt flow in VSD and PDA. However, LA enlargement from increasing volume overload is not consistently reflected in the echo A-P diameter as LA geometry changes. Moreover, transducer beam angulation affects the LA/Ao ratio determination. The latter may not be reliable for estimating shunt size in VSD.

DETECTION OF ABNORMAL SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR (LV) FUNCTION IN CHILDREN WITH AORTIC STENOSIS (AS) BY COMPUTERIZED ECHOCARDIOGRAPHIC ANALYSIS Mark J. Friedman, MD; David J. Sahn, MD, FACC; Harry Burris; Hugh D. Allen, MD, FACC; Stanley J. Goldberg, MD, FACC; Dept. of Ped., U. of Az., Tucson, Az.

Although echocardiograms from children with AS show hyperdynamic LV wall motion patterns, the hypertrophied ventricle is functionally abnormal during contraction and relaxation. In order to study systolic (SYS) and diastolic (DIAST) LV function, septal and posterior wall echo traces were digitized and analyzed by mini-computer in 52 normal (NL) children and 30 age-matched children with cath proven AS, with (13) and without (17) coarctation. Compared to the NL children, the AS patients had statistically smaller and thicker walled LV's and increased LV minor axis fractional shortening (△D) (AS mean △D=41±3%(SE)). Continuous minor axis dimension traces (D) and dD/dt were plotted. The traces allowed measurement of isovolumic contraction time, pre-ejection period, ejection time (ET) and diastolic lengthening time, as well as the maximal velocity of shortening (MVS) and of lengthening (MVL) in mm/sec. ET (NL=0.28±.07) was abnormally prolonged in the AS children after heart rate (HR) correction (111±4%)(p<0.01). MVS (NL=96.3±3mm/sec) was depressed to 84.0±5mm/sec in mild and to 76.8±11mm/sec in severe AS. MVL (NL=115.4±4mm/sec) was also depressed in mild (98.5±12mm/sec) and in severe (85.5±13mm/sec) disease (all p<0.005). Both MVS and MVL were independent of HR and LV size. The study provides a comprehensive method and new indices (MVS and MVL) for analysis of LV function from a ventricular M-mode echo alone and documents abnormal SYS and DIAST LV performance in chidren with AS and LV hypertrophy.



USE OF CONTRAST ECHOCARDIOGRAPHY FOR EVALUATION OF RIGHT VENTRICULAR HEMODYNAMICS IN THE PRESENCE OF VENTRICULAR SEPTAL DEFECTS. Gerald Serwer MD, Brenda Armstrong MD, Douglas Sherman BS, Woodrow Benson MD, Page Anderson MD, Sam Edwards MD, Duke University, Durham, North Carolina.

Intracardiac blood flow is altered as a consequence of VSDs. Varying sized VSDs produce different flow patterns across the defect which can be visualized by peripheral injection echocardiography (PIEC) allowing estimation of RV pressure and pulmonary resistance. Forty-five patients (pts.) ages 2 wks. to 16 yrs. underwent PIEC within 24hrs. of cardiac cath. Pts. were placed in 1 of 5 groups. Group 1, N=17, no VSD (N=8) or small VSD (N=9) with Q_p/Q_s<1.5:1 and RV pressure <½ systemic had appearance of echo-dense material (EDM) in the RV only, none appeared in the LV. Group 2, N=8, VSD with Q_p/Q_s>2:1 and RV pressure 60% to 80% systemic had appearance of EDM in th LV anterior to the mitral valve (MV) at the peak of MV opening. Time from QRS to appearance of EDM in the LV divided by the R-R interval (AT/RR) was .62 to .69 and was independent of heart rate. EDM returned to the RV in late diastole with none appearing in the aorta. Group 3, N=6, VSD with Q_p/Q_s >3:1, systemic RV pressure, Rp≤5units/M^2, and no PS had appearance of EDM in the LV anterior to the MV with subsequent appearance in the aorta. AT/RR was .63 to .69 unchanged from group 2. Group 4, N=12, tetralogy of Fallot, had appearance of EDM in the LV early in diastole with AT/RR .53 to .59, significantly less than in group 3 (P<.001). EDM appeared in the aorta. Group 5, N=2, had systemic RV pressure, no PS, and Rp>16units/M^2. The flow patterns were as in groups 3 & 4 but AT/RR was .42 to .47, less than group 4 (P<.01). PIEC allows estimation of RV pressure and evaluation of increased resistance to pulmonary flow in the presence of VSDs. It provides a minimally invasive method for serial evaluation of pts. with VSDs and separation of pts. with normal versus high pulmonary vascular resistance.

MONDAY, MARCH 6, 1978
PM
RESULTS OF CORONARY SURGERY
3:30 to 5:30

IMPROVED SURVIVAL BEYOND 5 YEARS IN 1108 PATIENTS UNDERGOING CORONARY BYPASS
Gerald M. Lawrie, M.D., George C. Morris, Jr., M.D.,FACC, Jimmy F. Howell, M.D., FACC, Tomas Tredici, Don W. Chapman, M.D., FACC, Baylor College of Medicine, Houston, Texas.

To determine truly late survival after coronary bypass (CAB), 1108 consecutive patients (pts) were contacted 60-76 months after operation. There were 985 males (89%). The mean age was 50.1 years (range 26-75 years). Operation was performed for angina with coronary lesions >70% in 1067 pts (96.3%). Forty-one pts (3.7%) had congestive heart failure without angina and in 233 pts (21%) both were present. Unstable angina was present in 144 pts (13%). Previous myocardial infarction had occurred in 654 pts (59%). Single vessel disease was present in 196 pts (17.6%), double vessel in 413 pts (37.3%), triple vessel in 416 pts (37.6%) and left main stenosis >50% in 83 pts (7.5%). Operative mortality was 4.1% (45 pts) overall. Excluding pts with left main disease (LM) overall crude 5 year survival was 90.0% (927/1025). Survival by subgroups was: one vessel-94.0% (184/196) overall and 95.6% (152/159) in pts with good ventricular function (GLV); two vessel-91% (376/413), GLV-94.8% (294/310); three vessel-88.2% (367/416), GLV-91.7% (244/277); left main 84.3% (70/83), GLV-94.2% (49/52). Graft patency in 147 pts was 87.0% (249/287) and 94% (138) pts had at least one patent graft. Survival of a sample of normal population of identical age and sex was 92.7%. Thus, surgically treated patients with GLV regardless of their anatomic lesions have been restored to normal survival rates. With poor ventricular function, survival is impaired but is still superior to reported results of medical treatment. We feel these results indicate that CAB prolongs life.

RE VASC ULARIZATION O F THE RIG HT CORONARY ARTERY WITH STENOSIS LESS THAN 70%
Hillel Laks, MD, FACC; George C. Kaiser, MD, FACC; Hendrick B. Barner, MD, FACC; J. F. Gerard Mudd, MD, FACC; John E. Codd, MD; and Vallee L. Willman, MD Saint Louis University School of Medicine, Saint Louis, Missouri 63104

This study was undertaken to evaluate bypass grafts to the right coronary artery (RCA) with < 70% stenosis. Flows and patency were compared in three groups distributed equally during the years 1971-1975. Group I, RCA stenosis< 50%, II, stenosis 51-69%, and III, stenosis> 70%. All had catheterization at six months, 105 at one year, 52 at three years and 28 at five years.

RCA Stenosis	No.	FLOW ml/min	PATENCY No.	%	FLOW<40ml/min No.	%
< 50%	23	70	21	91%	7	32%
51-69%	35	73	26	74%	9	25%
> 70%	112	72	92	82%	23	21%

There was no significant difference between the mean RCA size measured by probe, mean intraoperative graft flow and graft patency between other vessels was similar to RCA grafts in all groups. The proximal lesions progressed in 15 (83%) in group I, 17(61%) in group II, and 35 (85%) in group III. Among 57 patients with non grafted RCA stenosis < 50%, 29(51%) show progression which was less than that seen in group I(p<0.01). Conclusion: The severity of RCA stenosis does not influence vein graft patency or flow. Bypass to a RCA with<50% stenosis results in apparent increased proximal disease progression.

THE EFFECT OF SURGICAL VERSUS MEDICAL THERAPY ON SURVIVAL OF PATIENTS WITH CORONARY DISEASE. A MATCHED PAIR ANALYSIS OF NON-RANDOMIZED COHORTS

Karl E. Hammermeister, MD, FACC; Timothy A. DeRouen, PhD; Harold T. Dodge, MD, FACC. VA Hospital and University of Washington, Seattle, Washington

To validly compare survival of non-randomized cohorts of medically and surgically treated coronary disease patients, it is essential that the two cohorts be similar in characteristics relevant to survival. Univariate screening was performed on over forty variables from clinical examination, ECG, coronary arteriogram, and quantitative analysis of left ventricular angiogram on 550 medically treated and 913 surgically treated coronary disease patients who have been followed an average of 30 months in Seattle Heart Watch. This was followed in order by stepwise discriminant analysis and Cox's regression analysis resulting in seven variables independently predictive of survival. These are, in order of significance: ejection fraction, ventricular arrhythmia on resting ECG, age, heart murmur, left main stenosis, number of vessels with stenosis $\geq$70% (NVES70), and use of diuretic therapy. Each medically treated patient was paired to one surgically treated patient matched by all seven variables, resulting in 287 matched pairs. Statistically significant differences in survival were not seen in the 140 matched pairs with NVES70=1 or the small number of pairs (50) with NVES70=3. However, in the 97 matched pairs with NVES70=2, the surgical cohort had significantly better survival ($p=0.0002$) than the medical cohort with five year survival probability of 0.95±0.03 (SE) in surgical cohort and 0.76±0.05 in medical cohort. These results were confirmed by Cox's regression analysis of the total population. These data indicate that surgical therapy does prolong survival in comparable cohorts of patients with two vessel coronary disease.

EMERGENCY REVASCULARIZATION FOR UNSTABLE ANGINA

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One hundred consecutive patients had emergency revascularization for unstable angina and fulfilled the criteria of the National Cooperative Study Group. Single vessel disease was found in 19, double vessel in 32, and triple vessel in 49. Mean time from catheterization to surgery was one day. Early (30 day) mortality was 4% and perioperative infarction 17%. Complete revascularization was obtained in 69% of patients. After a mean follow-up of 36 months, four late deaths (4.3%) and three late infarctions (3.1%) occurred, and 78% of the survivors were asymptomatic. Fourteen patients had severe left main trunk obstruction with one early and two late deaths. If these are excluded, survival was 95%. Postoperative angiography in 47 survivors (mean interval 14 months) showed 86% graft patency. Twenty-seven patients with recent, new onset of unstable angina were contrasted with 59 who had an exacerbation of a previously chronic stable anginal state. The recent onset group showed markedly lower incidence of triple vessel disease, no early or late mortality, a perioperative infarction rate of 29.6%, and all but one infarction patient had surgery within 24 hours after catheterization. Three of the four early deaths occurred in patients who had revascularization within 24 hours following catheterization and showed a recent myocardial infarction at autopsy which antedated the surgery, despite ECG or enzymatic evidence of preoperative myocardial infarction. These results suggest that mortality and infarction rates may be improved when patients with unstable angina are stabilized for at least 24 hours prior to surgery to exclude myocardial infarction.

UNSTABLE ANGINA: THE CASE FOR OPERATION.

Gordon Olinger, MD, FACC, Lawrence Bonchek, MD, FACC, Michael Keelan, MD, Donald Tresch, MD, FACC, Ronald Siegel, MD. The Medical College of Wisonsin, Milwaukee, Wisconsin.

The NIH cooperative study of medical vs. surgical therapy for unstable angina (UA) reports 4 vs.5% hospital mortality and 10 vs. 18% early infarct rate. It concludes UA pts should be treated medically. Contrarily, our experience with UA indicates revascularization (CAB) is far safer than reported. From 7/75 through 3/77, 70 consecutive UA pts (42 High-Risk--in-hospital rest pain with reversible ischemic ECG changes, and 28 Low-Risk--new rest pain remitting upon hospitalization) had CAB. Historical, ECG, and catheterization data were similar; High-Risk pts, however, required high dose propranolol (39/42 pts 140 mg qd) and 1 needed additional intraaortic counterpulsation (IABC) for preop stabilization of ischemia. Proximal LAD (62 pts) and left main (12 pts) disease with abnormal LV function (35 pts) characterized UA pts. CAB (2.7 grafts/pt) was done with hypothermia and intermittent ischemic arrest. Complications included only 1 death (1.4%--transfusion reaction 3 days postop in a High-Risk pt recovering uneventfully) and 1 periop MI (Low-Risk). No pt needed inotropic support; 34 (49%) needed nitroprusside for postop hypertension. There are no late deaths up to 26 mos. We conclude 1) "prophylactic" preop IABC for UA, although advocated by some surgeons, is unnecessary; 2) the very low incidence of complications when UA--particularly High-Risk UA--is managed as outlined strongly supports CAB as definitive therapy; and 3) the therapeutic implications of large scale, randomized studies of medical vs. surgical therapy for UA are clinically pertinent only if their surgical results parallel those reported herein. Such results are also obtained by other surgeons and relate directly to intensive preop medical management combined with meticulous perioperative myocardial protection.

CHANGING CONCEPTS IN THE SURGICAL MANAGEMENT OF LEFT MAIN CORONARY ARTERY DISEASE

Henry J. Sullivan, MD, Roque Pifarre, MD, FACC, Donald Dixon, MD, John M. Moran, MD, Alvaro Montoya, MD, Sarah A. Johnson, MD, FACC, Adel El-Etr, MD and Rolf M. Gunnar, MD, FACC. Loyola University Medical Center, Maywood, Illinois

Since June 1970, 196 patients with significant main left coronary artery stenosis have undergone surgery. Our experience with this condition may be divided chronologically into three phases. PHASE 1: 89 patients. Hemodynamic instability with frequent hypertension during induction of anesthesia characterized this group. Nine (10%) patients required urgent institution of cardiopulmonary bypass (CPB) for acute left ventricular failure. Operative mortality was 11% (10 patients). PHASE 2: 55 patients. Intra-aortic balloon counterpulsation (IABC) was instituted prior to surgery. Only one patient required urgent CPB. Operative mortality was 1.5% (1 patient). PHASE 3: 52 patients. Anesthetic management was characterized by administration of intravenous nitroprusside or nitroglycerine and monitoring of pulmonary (PA) pressure. No patients required urgent CPB and there was no operative mortality. Anesthetic induction is a critical time in the surgical management of patients with significant left main coronary stenosis. Our experience suggests that hemodynamic stability during this period may be achieved by IABC or by pharmacologic unloading of the left ventricle accompanied by monitoring of PA pressure.

INFLUENCE ON LATE SURVIVAL OF GRAFT STATUS AND DEGREE OF CORRECTION FOLLOWING AORTOCORONARY BYPASS GRAFT SURGERY

Jacques Hermann, MD; Frederico Corbara, MD; Jacques Lespérance, MD; Martial G. Bourassa, MD, FACC; Lucien Campeau, MD, FACC, Montreal Heart Institute, Montreal, Quebec, Canada

In 807 patients (pts) having pure aortocoronary bypass graft surgery among our first 1000 pts, the 6 year late survival (excluding deaths within the first month) was not influenced by the degree of correction. It was suspected that this might be explained by the high graft attrition of 25% during the first year. Survival was therefore determined after the first year in 65 pts in whom correction was still optimal as determined by angiographic studies obtained 1 year after surgery (all coronary arteries with stenosis ≥70% successfully bypassed), and in 267 pts with incomplete correction at angiography (N156) or at the time of surgery (N111). The 6 year late survival (6 yr LS) was 98.4±3.2% for the pts with optimal correction as compared to 83.2±6.4% for pts with incomplete correction ($p<0.025$). The 6 yr LS (after the first year) was 94.1±4.6% in 113 pts in whom all grafts were patent, as compared to 70.4±16.8% in 38 pts whose grafts were all occluded ($p<0.01$). 40 pts with at least 1 graft patent and 1 occluded had a 6 yr LS of 87.2±12.0%.

In conclusion, late survival is greatly influenced by the degree of correction and graft status 1 year after surgery.

LONG-TERM BENEFITS OF MYOCARDIAL REVASCULARIZATION (MR)

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From January, 1970 through June, 1977, 1541 patients received isolated coronary artery bypass grafts. Operative mortality was 2.6%. Actuarial five-year survival was 92.8%. Cumulative graft patency rates were 92.3% at one month, 85.8% at one year, 82.4% at three years and 78.5% at five years. Survival rate for single vessel disease was 97.7%. In multivessel disease, survival increased with the number of grafts used: single (90.6%), double (91.7%), triple or more (92.9%). Late myocardial infarction occurred in 3.3% of patients. Not only does MR appear to be of long-term benefit in relief of angina, but also it appears to offer favorable results in longevity and low incidence of late myocardial infarction.

MONDAY, MARCH 6, 1978
PM
ANGINA PECTORIS: CLASSICAL AND VARIANT
3:30 to 5:30

DECREASE IN MYOCARDIAL OXYGEN SUPPLY AS A MECHANISM IN RESTING AND NOCTURNAL ANGINA WITH ST DEPRESSION: HEMODYNAMIC EVIDENCE

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The mechanism of resting or nocturnal angina (AR) with ST depression (ST↓) is uncertain relative to a primary change in myocardial oxygen (MO_2) supply or demand. The temporal sequence of changes in systemic (BP) and pulmonary artery (PAP) pressures and lead V5 of the ECG, continuously recorded on tape for 11-43 hrs in 18 patients (pts) with history of AR and exertional angina, was therefore analyzed. Cardiac index (CI) was measured by Swan-Ganz thermodilution catheter every 2 hrs and at onset and at relief of AR. In 7 pts with >75% obstruction in 2-3 major coronary vessels and chest pain acceptable and treated as ischemic, there were no ECG or hemodynamic changes during pain. The nature of pain in these pts remains uncertain; it may be nonischemic in origin. Its response to nitroglycerin was poor, delayed and variable. In contrast, in each of the remaining 11 pts, AR was preceded by ST↓ and by marked increases in systolic PAP (25±1.1 vs 48±4.0 mmHg; $p<0.001$) and diastolic PAP (11±0.8 vs 27±1.7 mmHg, $p<0.001$). Stroke index was decreased at onset of pain (32.1±2.5 vs 27.7±1.9 ml/beat/m^2, $p<0.001$). In 7 of these pts BP increased significantly coincident with the ECG changes. In 4 pts who had the highest systemic vascular resistance (SVR), BP fell or did not change; 3 of these 4 pts had the lowest CI. Heart rate (HR) did not change significantly. Pain was relieved promptly in all cases by nitroglycerin. Since the HRxBP product (index of MO_2 demand) did not increase prior to the onset of ischemia, the data suggest that these cases of AR are due to a primary decrease in MO_2 supply.

HYPOXIC CORONARY CONTRACTION MEDIATED BY BETA$_2$ ADRENERGIC RECEPTORS

Philip D. Henry, MD, FACC; Mitsuhiro Yokoyama, MD; Steven Fisher, Washington University, St. Louis, Missouri

Hypoxia has been shown to produce in isolated canine coronary arteries transient relaxation and subsequent sustained contracture. To define the mechanism underlying contracture, helical coronary arterial strips ($n = 61$) mounted isometrically for tension recording were equilibrated in deoxygenated Krebs buffer for 5 min and exposed to cumulative concentrations of adrenergic antagonists or agonists. The α-blockers phenoxybenzamine (5 arteries), phentolamine, and prazosin (10 arteries each) did not attenuate contracture in concentrations up to 10^{-5} M. The α-agonists phenylephrine and methoxamine up to $5x10^{-5}$ M did not enhance contracture. In contrast, L-propranolol, a nonselective β-blocker, and butoxamine, a vasoselective (β_2) blocker, evoked dose-dependent relaxations and, at a concentration of 10^{-6} M, completely suppressed the contractures (15 arteries). Isoproterenol, a nonselective β-agonist, and soterenol and salbutamol, β_2-selective agonists, augmented contracture in a dose-dependent manner between 10^{-9} and 10^{-6} M, the highest doses producing at least threefold increases in tone (20 arteries). The cardioselective (β_1) blockers practolol, metoprolol, and paraoxprenolol failed to reduce contracture in concentrations up to 10^{-6} M (11 arteries). Thus, coronary arteries possess β_2-receptors which mediate hypoxic contracture. Results help to explain why propranol, but not practolol, increases perfusion in acutely ischemic canine myocardium.

MYOCARDIAL COMPROMISE AND SUDDEN DEATH IN ABERRANT CORONARY ARTERY ORIGIN FROM THE AORTA

Richard R. Liberthson, MD; Robert E. Dinsmore, MD, FACC; Peter C. Block, MD, FACC; Gerald M. Pohost, MD, FACC; and H. William Strauss, MD, Massachusetts General Hospital, Boston, MA

Aberrant coronary artery origin from the aorta (Ao) may lead to myocardial compromise or sudden death because of proximal obstruction of the aberrant coronary artery (AA) if it passes between the aorta and the right ventricular infundibulum (RVI). Seventeen patients (pts) with AA passing between the Ao and RVI are presented.

Of 12 pts with left AA, 4 pts (ages 1-16 yrs) had exertional sudden death, 2 had exertional syncope (ages 36 and 41 yrs) - 1 with no arrhythmia on Holter monitoring, and 1 with ventricular fibrillation (VF) following syncope. In these pts, the AA had proximal hypoplasia, kinking, or atherosclerosis. One pt had an anterolateral acute infarction (AMI), and 2 had ischemia on stress thallium scan. The other 6 pts with left AA were identified by angiography performed for chest pain (ages 54-63 yrs), 5 had diffuse atherosclerosis, but none had localized AA narrowing.

Of 5 pts with right AA, all were identified by angiography performed for chest pain. No pt had syncope, no pt had demonstrable AA narrowing, 4 had diffuse atherosclerosis, and 1 had inferior wall ischemia on stress thallium scan.

In summary, left AA may be lethal when the AA is severely narrowed, and should be considered in the evaluation of young pts with AMI, VF, or syncope. However, in the older pt, longevity itself generally attests to the absence of critical AA compromise. In right AA, proximal AA narrowing is rare as are clinical sequelae.

TRANSIENT ST SEGMENT ELEVATION IN UNSTABLE ANGINA: PROGNOSTIC SIGNIFICANCE.

Gary D. Plotnick, MD and C. Richard Conti, MD, FACC, Johns Hopkins University and V.A. Hospital, Baltimore, Maryland and University of Florida, Gainesville, Florida.

The prognostic significance of the direction of ST segment shift was examined in 82 consecutive patients (pts) with unstable angina (UA) defined as rest angina with transient ECG abnormalities and no enzyme rise. Eighteen pts with transient ST segment elevation (ST↑) with pain were followed for 66.3 months (range 42-84) (Group I) and sixty-four pts with transient ST segment depression (ST↓) were followed for 58.2 months (range 24-82)(Group II).

Based on life table analysis, one, three and five year survival was 75%, 75% and 68% respectively for Group I and 77%, 72% and 67% for Group II. In those pts receiving only medical therapy, survival was 73%, 73% and 64% for Group I and 71%, 71% and 66% for Group II. Non-fatal myocardial infarctions occurred in 3 of 12 survivors in Group I and 8 of 37 survivors in Group II.

Mortality in each group was related to the extent of coronary artery disease and left ventricular function and not the direction of the ST segment shift. Thus, pts with UA and transient ST↑ do not have a worse prognosis than patients with UA and transient ST↓.

CORONARY ARTERY SPASM INDUCED BY THE COLD PRESSOR TEST.

Albert E. Raizner, M.D., FACC, Tetsuo Ishimori, M.D., Robert A. Chahine, M.D., FACC, Nasiruddin Jamal, M.D., Baylor College of Med. & V.A. Hospital, Houston, Texas

The Cold Pressor (CP) test has been shown to reflexly increase coronary vascular resistance. To determine whether this reflex response might be of clinical importance, we performed the CP test in 17 patients (pts) with chest pain syndromes undergoing coronary arteriography. Clinically, 6 pts had classical angina, 8 had atypical chest pain and 3 had Prinzmetal's variant angina.

Following CP stimulation, (1 minute hand-immersion in ice water), aortic systolic pressure rose 20.7 ± 2.9 (mean ± SE) mmHg ($P < .01$) and heart rate increased 4 ± 2 beats/min (NS). Coronary artery spasm resulting in complete obstruction or critical coronary artery narrowing was observed in 4 of the 17 patients (incidence of 24%). Two of the 3 patients with Prinzmetal's angina developed spasm (complete occlusion of the anterior descending in one, subtotal right in the other) with chest pain or ischemic EKG changes. The third Prinzmetal pt. had been given isosorbide dinitrate prior to the study and did not manifest spasm with CP or with ergonovine. Two of the patients thought to have classic angina also manifested CP-spasm: One pt. had recurrence of previously observed spontaneous spasm of the anterior descending with CP, and one pt. with unstable, resting angina who had no critical coronary lesions developed critical right coronary spasm with CP. All CP-induced spasm occurred in areas of preexistent disease. No complications resulted from CP.

Thus, CP may be an important and safe provocative test for identifying those patients with ischemic heart disease in whom coronary artery spasm may be playing a significant role.

VARIANT ANGINA:CORONARY ANGIOGRAPHIC PATTERNS AND RESULTS OF MEDICAL AND SURGICAL THERAPY IN 42 CONSECUTIVE PATIENTS

Allen Johnson,MD FACC; Hilary Stroud,MD; WVR Vieweg,MD FACC; John Ross, Jr.,MD FACC, Univ of Calif, San Diego,Ca.

In 42 patients (pts) with variant angina (VA), coronary (C) angiographic patterns were correlated with therapeutic responses over an average follow-up period of 21 mos. 24 pts had rest pain alone; 18 also had exertional angina. 11 pts (24%) had no significant C obstruction [normal coronaries (Grade 0) in 4, and minor luminal irregularities (Grade 1) in 7]. 31 had significant atherosclerotic obstruction [greater than 75% narrowing (Grade II)]; only 1 artery was involved in 16 pts, and multiple vessel involvement in 15. Rest angina only was present in 9 of the 11 (82%) with Grade 0 or 1, whereas 16 of the 18 (89%) with both rest and exertional angina had Grade II disease. C artery spasm was documented in 8 pts, of whom 4 had Grade 0, 3 had Grade 1, and 1 had Grade II disease; no pt had pain and ST segment elevation during cath without documented spasm. Only 1 of the 42 pts had died during follow-up. 27 pts had C artery bypass grafting, including 3 with spasm; of the latter pts, 1 had Grade II, and 2 had Grade I associated with pain and refractory arrhythmias. No pt treated surgically has had recurrence of VA or serious arrhythmias. Of 15 pts managed medically with nitrates, 7 continue to have symptoms or have had myocardial infarction; 3 of these pts had Grade II and 4 Grade 0 or Grade I disease. We conclude: (1) the clinical presentation of VA does not allow accurate prediction of coronary anatomy, and C arteriography should be performed prior to planning therapy in all pts; (2) C spasm plays a significant role both in pts with normal C arteries and those with various degrees of atherosclerosis; (3) surgical treatment should be considered in all pts with significant atherosclerotic obstructions, and in pts without significant obstruction refractory to medical treatment.

LIDOFLAZINE TREATMENT OF STABLE ANGINA PECTORIS: A PLACEBO CONTROLLED DOUBLE-BLIND RANDOMIZED TRIAL

William Shapiro,MD, FACC; Janet Park, Medical Service, VAH and Southwestern Med. Sch. Dallas, Texas.

Lidoflazine, a long-acting vasodilator, was evaluated in 39 male patients (pts). They were required to have at least 5 attacks of typical angina pectoris per week, a normal electrocardiogram at rest, and at least 1 mm ST segment depression 80 msec after J point during bicycle exercise (ETT). A 3 month single-blind placebo phase was followed by a 4 month double-blind period in which 18 pts were randomized to placebo and 21 to active drug taken tid. Diaries of angina frequency and nitroglycerin (NTG) consumption were kept. ETT were performed at entry, twice during the single-blind phase and 3 times during the double-blind phase. All control data were averaged and compared to data obtained at the end of the double-blind period. Five pts (2 lidoflazine; 3 placebo) did not complete the study because of onset of instability. There were no drug-related adverse reactions. Lidoflazine administration decreased angina frequency 23.1%, $p<0.008$, while placebo pts had an increase of 12.3%, $p<.4$. The median weekly NTG consumption decreased by 46.8% in the lidoflazine pts, $p<04$, but increased by 4% in the placebo pts, $p<.8$. The median work tolerance during ETT increased by 50% in the lidoflazine pts, $p<006$, and decreased 6.1% in the placebo pts, $p<.7$. The median heart rate at individually comparable exercise levels decreased by 2.7 beats per minute in the lidoflazine pts and by 6.7 in the placebo pts. Since lidoflazine treatment improved both the anginal syndrome and work tolerance, it should be useful as a long-acting, well tolerated, anti-anginal agent. It may provide particular benefit to pts intolerant of beta-blockade, and probably to those who are not suitable candidates for bypass surgery.

SAFETY AND EFFICACY OF CONTINUED PROPRANOLOL ADMINISTRATION THROUGH CORONARY BYPASS SURGERY

Harisios Boudoulas, M.D.,FACC; Gary L. Snyder, M.D.; Richard P. Lewis, M.D.,FACC; Robert E. Kates, Ph.D.; Panayotis E. Karayannacos, M.D.; John S. Vasko, M.D., FACC, Departments of Medicine and Thoracic Surgery, The Ohio State University Hospitals, Columbus, Ohio.

It is widespread practice to discontinue propranolol (Pr) at least 24 hours prior to coronary bypass surgery (CBS) to avoid unwanted hemodynamic effects. However, abrupt discontinuation of Pr may result in unstable angina, acute myocardial infarction (MI), or sudden death. We have recently demonstrated a transient hypersensitivity to adrenergic stimulation in normals 24-48 hours after abrupt withdrawal of Pr. Since increased adrenergic tone is present in the perioperative period, we postulated that Pr should not be discontinued. Thirty patients undergoing CBS were studied. Pr was discontinued 4-10 hrs before surgery and restarted within 24 hours. Nineteen patients had a prior MI, 8 had a subnormal ejection fraction, and 24 required multiple bypass. Twenty-four hour urinary epinephrine and norepinephrine was measured the day before surgery and was dramatically increased at 120± 30 µg/24 hrs, (normal 39±4 µg, $p<0.01$). Plasma Pr one hr before surgery was 40±8 ng/ml. There were no deaths and only 4 perioperative MI (13%). This compares to a 28% incidence previously reported from our institution at which time Pr was routinely discontinued at least 24 hrs before CBS. There were no hemodynamic complications attributed to Pr. Thus, administration of Pr up to 4 hrs before surgery, and prompt reinstitution (within 24 hrs) is safe. In view of the excessive adrenergic tone both the day before and after CBS, and the known hypersensitivity to adrenergic stimulation following abrupt withdrawal of Pr, it would appear that Pr should be continued through CBS.

MONDAY, MARCH 6, 1978
PM
RESEARCH IN MYOCARDIAL INFARCTION
3:30 to 5:30

DIRECT EVIDENCE FOR THE BENEFICIAL EFFECT OF PROPRANOLOL ON MYOCARDIAL ISCHEMIA FOLLOWING CORONARY ARTERY OCCLUSION

David Hillis,MD, Shukri Khuri,MD, Robert Kloner,MD,PhD, Donald Tow,MD, Ernest Barsamian,MD, Peter Maroko,MD,FACC, Eugene Braunwald,MD,FACC,Depts of Surg, Nuc Med & Med, W Roxbury VA Hosp and PBBrigham Hosp, Harv Med Sch,Boston,MA

Using largely indirect methodology, propranolol(P)has been shown to reduce myocardial ischemia(I)after coronary artery occlusion(CAO). To assess its direct effect on myocardial oxygen(PmO_2)and carbon dioxide($PmCO_2$)tensions during I, 2 successive 10 minute CAOs were performed 1 hour apart in 14 dogs: 7 were controls(C) and 7 received P, 2 mg/kg iv, 10 minutes before CAO#2. PmO_2 and $PmCO_2$ were recorded continually with a mass spectrometer while regional myocardial blood flow(RMBF)was measured by the Xe^{133} washout technique. PmO_2 and $PmCO_2$ did not change with CAO or P in nonischemic areas. In C PmO_2 fell and $PmCO_2$ rose in the zone of I similarly with both CAOs, and RMBF was unchanged.

Control	CAO#1	CAO#2	Δ(CAO#1-CAO#2)
ΔPmO_2 (mmHg)	7.0±1.7	8.0±1.5	- 1.0±0.7
$\Delta PmCO_2$ (mmHg)	27.6±4.4	26.8±4.1	+ 0.8±1.5
RMBF(cc/100g/min)	29.3±7.7	24.8±4.4	+ 4.5±6.6
Propranolol			
ΔPmO_2 (mmHg)	10.4±1.8	8.5±1.8	+ 1.9±0.9
$\Delta PmCO_2$ (mmHg)	41.8±7.1	22.2±4.0	+19.6±3.7
RMBF(cc/100g/min)	27.4±9.2	20.0±7.2	+ 7.4±2.6

In contrast, the CAO after P caused less fall in PmO_2 ($p<0.05$) and less rise in $PmCO_2$ ($p<0.001$) than did CAO#1, despite a lower RMBF ($p<0.05$). This study, based on direct measurement of myocardial O_2 and CO_2 tensions, demonstrates a reduction of ischemia by propranolol despite a fall in blood flow to the ischemic tissue and offers a rational basis for use of propranolol in the treatment of ischemic injury following coronary occlusion.

PROSTAGLANDIN INHIBITION INCREASES INFARCT SIZE AFTER CORONARY ARTERY OCCLUSION IN CONSCIOUS DOGS.

Bodh I. Jugdutt, MBChB; Lewis C. Becker, MD, FACC; Bernadine H. Bulkley, MD, FACC; Grover M. Hutchins, MD. Johns Hopkins University, Baltimore, Maryland.

Prostaglandins (PG) are released during myocardial ischemia. We have shown that inhibition of synthesis of PG with indomethacin (IN) prevents the early increase in collateral blood flow which normally occurs after acute left circumflex coronary artery occlusion in conscious dogs. To determine whether this effect on collateral flow influences infarct size, we studied the area of myocardial necrosis 2 days after acute left circumflex coronary artery occlusion in 18 conscious dogs instrumented 2 weeks previously. Eleven dogs were given IN (7.5 mg/Kg) 20 minutes before occlusion, and 7 were used as controls (C). Coronary blood flow was measured pre and post-occlusion by 10 µ radioactive microspheres. The region at risk was determined post-mortem by selective coronary angiography (13 dogs) or coronary perfusion with dye (5 dogs), and confirmed by flow criteria. Myocardial necrosis (N) was assessed by planimetry of weighed slices of the left ventricle (LV) and expressed in grams (g) and as a percentage of the mass of the region at risk (R).

	LV mass (g)	R (g)	N (g)	N/R (%)
C	85.9	41.5	12.7	27.2
IN	93.3	47.4	25.1**	49.2*

*$p < 0.02$ and **$p < 0.05$ respectively compared to control

Thus, IN given before occlusion leads to an increase in the area of myocardial necrosis within the zone at risk after coronary occlusion. This suggests that PG play a role in determining ultimate infarct size.

SERIAL IN-HOSPITAL MYOCARDIAL SCINTIGRAPHIC ALTERATIONS OF LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTS

Don Twieg, MS; Jose Pulido, MD; James Doss, MS; Frederick Bonte, MD; Robert W. Parkey, MD; James T. Willerson, MD, FACC, University of Texas Health Science Center, Dallas, Tx.

In vivo labeling of red blood cells with technetium-99m pertechnetate was used to obtain serial myocardial scintigrams (S) in the CCU in 69 pts with acute myocardial infarcts (AMI) to determine the frequency with which significant alterations in LV ejection fraction (EF), occur during hospitalization. At least 2 and in many instances 3 S were obtained over a 2½-3 week period. S were obtained in modified LAO and RAO views to compute ventricular volumes by established geometrical methods. S accuracy was established by a good correlation with angiographic contrast ventriculograms obtained in 19 pts in whom LV EF correlated (r=0.90). In the 69 pts those with CHF had LV EF of 39±13% (S.D.), those without CHF 53±14% ($p<.001$). Thirty-three pts had anterior, 28 inferior and 8 subendocardial AMI. Twenty-one with anterior MI, had "donut" (central scintigraphic defect surrounded by intense ^{99m}Tc-PYP uptake) ^{99m}Tc-PYP S. The initial mean LV EF was 44±13% with anterior, 55±14% with inferior and 59±12% with SEMI; LV EF was significantly lower after anterior MI ($p<0.01$). The mean initial LV EF was 40±13% in pts with anterior MI and the "donut" pattern. With anterior MI, LV EF decreased serially by 10% or > in 12 (incidence of 36%) and by 20% or > in 10 (incidence of 30%). With inferior MI, LV EF decreased serially by 20% or > in 7 (25%). After SEMI, LV EF decreased by 20% or > in 2 of 8 pts with serial S. With "donut" anterior MI, LV EF decreased by 10% or > in 10 (50%) and by 20% or > in 7 (33%). Alterations in medications, intravascular volume, heart rate and blood pressure did not appear to entirely explain these changes. Correlation of serial S changes in LV EF with ECG, enzymes and clinical history to detect extension of MI revealed several pts without other clinical evidence of infarct extension. The data suggest that serial S measurement of LV EF during the acute and immediate recovery period after AMI provides important functional information that may be utilized for prognostic and therapeutic considerations.

WALL THINNING, STRESS AND PERFUSION OF ACUTELY ISCHEMIC MYOCARDIUM: COMPARATIVE EFFECTS OF NITROPRUSSIDE AND NITROGLYCERIN.

James Martins, MD, Richard Kerber, MD, FACC, Melvin Marcus, MD, FACC, CV Cent and CV Div, Univ of Iowa Hosp, Iowa City, Iowa

Nitroprusside (NP) has been found to be beneficial in acute myocardial infarction in some studies, but deleterious (decreased perfusion and increased myocardial injury) in others. The purpose of this study was to evaluate the effects of NP on acutely ischemic left ventricular wall thinning, wall stress (WS) and perfusion (P), and to compare NP with nitroglycerin (NG). Ventricular dimensions and wall thickness at end-diastole (WTd) and end-systole (WTs) were determined echocardiographically in 14 open-chest dogs. After circumflex coronary occlusion (CCO) systolic posterior wall thinning (WTs/WTd <1.0) occurred. End-systolic WS was estimated from simultaneous echo and pressure measurements: WS = pressure x ventricular diameter ÷ wall thickness. P was measured by 8 μ radiolabeled microspheres 30 minutes after CCO. Control P was 131±13 ml/100g/min; endo/epi ratio was 1.05 ±.06. After CCO NG or NP was infused to lower mean arterial pressure (MAP) 15%. Results (±SEM, *=p<.05 vs CCO):

	CCO	NP (N=7)	CCO	NG (N=7)
MAP (mmHg)	89±4	70±6*	95±7	80±7*
Heart rate (b/min)	149±5	152±12	150±10	145±9
Posterior WTs/WTd	0.94±.02	0.92±.03	0.89±.03	0.96±.05
Posterior WS	360±48	195±21*	446±60	273±40*
Posterior P (ml/100g/min)	43±16	40±8	39±11	37±14
Endo/Epi ratio	0.79±.06	0.87±.15	0.76±.03	0.71±.10

Conclusion: Both NP and NG reduced wall stress. With both drugs perfusion of the ischemia area was maintained despite the pressure reduction. Wall thinning was not exacerbated. Thus, both NP and NG should be of benefit in acute infarction.

THE NATURAL HISTORY OF MYOCARDIAL PERFUSION DEFECTS IN PATIENTS WITH UNCOMPLICATED MYOCARDIAL INFARCTION

Harischandra Karunaratne, MD; Sema Cantez, MD; Paul Harper, MD; Leon Resnekov, MD, FACC, University of Chicago Chicago, Illinois.

The evolutionary changes in the apparent perfusion defects following acute myocardial infarction (M.I.) can be readily studied with the short half-life perfusion imaging agent nitrogen-13 labeled ammonia ($^{13}NH_4^+$). In 18 patients (pts) who had an uncomplicated clinical course following an acute transmural M.I., the natural history of the perfusion defects was studied by serially imaging each patient 3-6 times in the first ten days. Fourteen pts had their initial images recorded <24 hrs, and 4 pts <36 hrs after onset of symptoms. All pts were imaged in the AP and LAO projections at the bedside using a standard γ-camera and tungsten collimation after injection of 20 mCi of $^{13}NH_4^+$. All patients showed perfusion defects corresponding to the ECG location of the M.I. in their initial images. Additional defects corresponding to electrocardiographically recognizable previous M.I.'s were seen in 6 pts. In 15 of the 18 pts, the perfusion defects were largest and most conspicuous in the initial images and on serial imaging the initial perfusion defects became smaller. Five showed improvement at 48 hrs and the others at 72 hrs or later. In 3/18 pts the images remained unchanged serially. It is concluded that serial myocardial imaging using $^{13}NH_4^+$ provides information of use to the clinician which correlates well with anatomical and cardiac effects of the lesion and that (a) perfusion defects (PD) are most conspicuous when imaging is performed early after M.I.; (b) PD either improve (15/18) or remain unchanged (3/18) in uncomplicated acute M.I., but none worsened; (c) The demonstrated natural history of changing PD limits the use of this approach for infarct sizing.

COMPARISON OF ELECTROPHYSIOLOGIC AND MECHANICAL EFFECTS OF MYOCARDIAL INFARCTION: CORRELATION OF THE PRECORDIAL MAP WITH GLOBAL AND REGIONAL EJECTION FRACTION

Denis E. Maddox, MD; James Muller, MD; J. Anthony Parker, MD; Roger Uren, MBBS; Jane Neill; B. Leonard Holman, MD, FACC; Peter F. Cohn, MD, FACC, Harvard Medical School and Peter Bent Brigham Hospital, Boston, MA.

To compare the electrophysiologic and mechanical effects of acute myocardial infarction, global left ventricular ejection fraction (LVEF) and regional ejection fraction (REF) derived from 6 x 10^6 count gated radioangiocardiograms were compared with the sum of R wave voltage (ΣR) and the number of Q waves (#Q) determined from 35 lead precordial ECG maps in 19 patients. LVEF and REF (anteroapical region) were calculated from computer generated time activity curves, following equilibrium imaging (Anger camera) of Tc-99m labeled cardiac blood pool from a modified left anterior oblique projection. ΣR and #Q were determined from precordial ECG maps of 4 normal patients, 11 patients with isolated anterior wall myocardial infarction (AMI) and 4 patients with both AMI and diaphragmatic myocardial infarction (DMI). ΣR and #Q correlated closely with LVEF (r=.80 and r=-.74, respectively). Stronger correlation was noted with REF (r=.86 and r=-.75). Exclusion of 4 patients with DMI improved correlations of ΣR and #Q with both LVEF (r=.88 for ΣR, r=-.85 for #Q) and REF (r=.93 for ΣR, r=-.86 for #Q). Thus, there is agreement between noninvasively determined LVEF and precordial ECG maps in selected patients. Agreement can be substantially improved when REF (anteroapical region) is used instead of global LVEF.

RELATIONSHIPS BETWEEN THE SITE OF INFARCTION, INFARCT SIZE, AND MORTALITY

Hans D. Strauss, MD; H. Dieter Ambos; Burton E. Sobel, MD, FACC; Robert Roberts, MD, FACC, Washington University School of Medicine, St. Louis, Missouri.

Despite the conventional view that the increased mortality associated with anterior compared to inferior infarctions reflects infarct size, objective information characterizing the relationship between infarct size and the site of infarction is not yet available. Since inferior infarction may involve both right and left ventricles in contrast to the left ventricle alone with anterior infarction, lower mortality might be anticipated with comparable overall infarct size. Accordingly, we prospectively studied 258 patients with acute transmural infarction localized by ECG (anterior in 116 and inferior in 142). Mean age (62 and 61 years), heart rate (71 and 73 beats/min), systemic blood pressure (138/82 and 137/79 mm Hg) determined eight hrs after the onset of chest pain and infarct size index estimated enzymatically (24.2 ± 1.8 CK g-eq/m^2 BSA and 23.4 ± 2.2) were similar in patients with anterior and inferior infarction. Even when patients were subdivided into those with initial infarction (Group I) and those with infarction at least three months after a previous episode (Group II), the extent of anterior and inferior infarction was the same (Group I - 24.6 ± 2.2, n=110 and 25.9 ± 3.1, n=86, Group II - 23 ± 4.4, n=32 and 15.8 ± 3.5, n=30, p> .2). Thus, contrary to our initial expectations, infarct size was similar in patients with anterior or inferior infarction. The higher mortality associated with anterior infarction may in part be related to all the damage occurring in the left ventricle as opposed to its distribution in both ventricles with inferior infarction.

DETECTION, QUANTITATION, AND CONTRAST ENHANCEMENT OF MYOCARDIAL INFARCTION UTILIZING COMPUTERIZED AXIAL TOMOGRAPHY.

Charles B. Higgins, M.D.; Paul T. Siemers, M.D.; Walter Schmidt. University of California, San Diego, California.

No direct method exists which can detect the presence and assess the volume of myocardial infarction (MI). We evaluated the potential of computerized axial tomography (CAT) for these purposes in 40 dogs with 6 and 48 hour old MIs. The CAT scan detected MIs in the ex situ heart in all instances and differentiated subendocardial from transmural MI. Volume by CAT without contrast material, was 19% less than the true volume (determined by histochemical staining with nitrotetrazolium blue) but had a close linear relationship to the true volume (r=.97).

Administration of contrast material 5 minutes prior to cardiectomy produced positive enhancement of either the periphery or throughout both the 6 and 48 hour old MIs. The attenuation coefficient of contrast enhanced MIs was 12.3 ± 0.6 EMI units greater than normal myocardium. Fluorescence excitation analysis of tissue samples revealed a 2.5 to 4 X greater accumulation of contrast material in the MI compared to normal myocardium, lung, and skeletal muscle.

Thus, CAT has the potential for detecting and sizing MIs. The ideal imaging agent (contrast material) for the CAT scan is differentially accumulated in MI and should facilitate its detection.

MONDAY, MARCH 6, 1978
PM
CARDIAC FUNCTION
3:30 to 5:30

EFFECT OF CONCENTRIC HYPERTROPHY ON LEFT VENTRICULAR DIASTOLIC STRESS-STRAIN RELATIONSHIP.

Donald R. Ricci, MD; Kirk L. Peterson, MD, FACC; Shigetake Sasayama, MD; Dean Franklin; John Ross,Jr., MD, FACC Cardiology Division, University of California, San Diego, La Jolla, California.

The manner in which increased ventricular muscle mass alters dynamic compliance characteristics during diastole is not clear. To determine the effect of pressure overload hypertrophy on left ventricular(LV) stress(σ)-strain (ε) relationships, we analyzed chamber and myocardial force-length parameters at 5 msec intervals through diastole in the normal control (C) state and after concentric hypertrophy (CH) was induced by subtotal aortic constriction in 6 conscious dogs. All were previously instrumented with a high fidelity pressure manometer and sonomicrometers for measuring minor equator LV internal diameter and wall thickness. After development of CH, LV wall thickness and muscle cross sectional area were increased ($p<.001$) while end-diastolic diameter remained constant. Deviation of the σ-ε relationship from a monoexponential curve occurred during rapid phases of filling, becoming more pronounced after CH. In 2 dogs, σ-ε curves during CH were shifted upward and to the left but were parallel to C curves,indicating an effect of increased muscle mass per se. However, in 4 dogs the relationship not only was shifted but also was steeper. Peak $d\sigma/d\varepsilon$ at end-diastole rose from 1100±280 gm/cm^2 in C to 3770±1080 gm/cm^2 during CH ($p<.03$, n=6), indicating increased muscle stiffness. Pressure(P)-diameter(D)analysis revealed similar changes in chamber stiffness to those of muscle;peak dP/dD at end-diastole rose from 9.1±.9 g/cm^2/mm in C to 21.2±5 g/cm^2/mm during CH ($p<.05$). Therefore, pressure overload hypertrophy: 1) usually, but not invariably, causes increased muscle stiffness; 2) creates parallel changes in chamber and muscle stiffness; 3) enhances viscous behavior during rapid ventricular filling.

EFFECT OF HYPOXIA ON MYOCARDIAL RELAXATION IN ISOMETRIC CAT PAPILLARY MUSCLE

William H. Frist; Igor Palacios, MD; Wm. John Powell, Jr., MD, FACC, Massachusetts General Hospital, Boston, Mass.

Myocardial relaxation is an energy dependent process which is important to normal cardiac function. However, hypoxia, which should interfere with this energy requiring process, has not been shown to impair myocardial relaxation. Data from previous studies indicate that hypoxia shortens relaxation time. These results may be misleading because 1) the traditional index to assess isometric muscle relaxation ($\frac{1}{2}$ time to relaxation or $RT_{\frac{1}{2}}$) reflects both changes in developed tension as well as relaxation and 2) the relaxation process is highly sensitive to temperature and previous papillary muscle studies have been conducted under hypothermic conditions. The present study examines the effect of hypoxia on the relaxation process of 31 isometrically contracting kitten papillary muscles at hypothermic (29°C) and normothermic (38°C) conditions using $RT_{\frac{1}{2}}$ and the peak rate of tension fall (-dT/dt), and -dT/dt normalized for instantaneous tension [(peak -dT/dt)/T and max (-dT/dt/T)]. Hypoxia at 29°C resulted in a shortening in $RT_{\frac{1}{2}}$ from 278±11 (SEM) to 230±17 msec ($p<.01$) and no significant changes in (peak -dT/dt)/T and max (-dT/dt/T). However, at 38°C hypoxia impaired myocardial relaxation as reflected in a prolongation of $RT_{\frac{1}{2}}$ from 101±6 to 126±8 msec ($p<.01$). This prolongation of $RT_{\frac{1}{2}}$ occurred in spite of a substantial fall in peak tension which by itself would tend to shorten the duration of $RT_{\frac{1}{2}}$. Further evidence for impaired relaxation with hypoxia at 38°C is reflected in the indices in which an attempt was made to normalize -dT/dt for tension; (peak -dT/dt)/T decreased from -15.4±0.7 to -11.0±0.8 sec^{-1} ($p<.01$) and max (-dT/dt/T) decreased from -25±1.8 to -13.8±0.9 sec^{-1}. In conclusion, the present study demonstrates that hypoxia impairs the relaxation process of cardiac muscle.

THE EFFECT OF CORONARY PERFUSION PRESSURE ON DIASTOLIC WALL STIFFNESS IN THE ISOLATED, BLOOD-PERFUSED DOG HEART.

James R. Mieszala, B.S.; Carl S. Apstein, M.D., FACC; Michael D. Yarnoz, M.D.; John J. Vecchione, M.D.; Helen R. Gilman, B.S.; C. Robert Valeri, M.D.; Robert L. Berger, M.D., Boston University School of Medicine, Boston, Ma.

Previous studies in the isolated buffer-perfused rabbit heart have shown that a change in coronary perfusion pressure (CPP) directly alters the passive diastolic stiffness of the left ventricle (LV). In this study an isolated blood-perfused dog heart was maintained at a CPP of 100 mmHg for 90 min. and passive filling curves were measured by slow filling of an intra-ventricular balloon at CPP=100 mmHg or during a transient (< 30 sec.) period of CPP=0. The passive filling curves of left ventricular end-diastolic pressure (LVEDP) vs. left ventricular end-diastolic volume (LVEDV) were near linear ($r > 0.98$) for an LVEDP range of 0-30 mmHg. The slope (Δ LVEDP/Δ LVEDV) was used to approximate the passive diastolic stiffness in 7 hearts.

Passive Diastolic Stiffness (Δ LVEDP/Δ LVEDV; mmHg/ml)

Perfusion Time	CPP=100 mmHg	CPP=0 mmHg
(30 Min)	1.08 ± 0.20	0.72 ± 0.11
(90 Min)	1.80 ± 0.16	1.20 ± 0.10

$p < .025$ for CPP=0 vs. CPP=100 at both perfusion times; $p < .05$ for t=30 min. vs. t=90 min. at both CPP.

After 90 min. of isolated perfusion, systolic performance deteriorated and an increase in passive diastolic stiffness occurred; however, the effect of CPP on passive diastolic stiffness was proportionally constant. These data show the effect of CPP on passive LV wall stiffness and indicate that LV diastolic filling and LVEDP at a given LVEDV can be influenced by the aortic or coronary perfusion pressure.

LEFTWARD SEPTAL DISPLACEMENT DURING RIGHT VENTRICULAR LOADING IN MAN: DEMONSTRATION BY TWO-DIMENSIONAL ECHO

James L. Weiss, M.D. F.A.C.C., Jeffrey A. Brinker, M.D., Donald L. Lappé, M.D., John L. Rabson, M.D., Warren R. Summer, M.D., Solbert Permutt, M.D., Myron L. Weisfeldt, M.D. F.A.C.C. Johns Hopkins Medical Institutions, Baltimore, Maryland.

It has been suggested that the right ventricle (RV) may restrain left ventricular (LV) filling; however, there is no direct evidence in man that RV loading alters LV diastolic configuration. We used the Mueller maneuver (forced inspiration against a closed airway) to increase RV loading, and evaluated septal dynamics and RV and LV dimensions in 9 normal semisupine men with phased-array, 2-dimensional echocardiography. End systolic and end diastolic (ED) frames in longitudinal and cross-sectional views of the ventricles were recorded at control and maximum early Mueller (EM) at 40-60 mmHg negative pressure. Acute leftward bowing of the septum seen at ED on cross-section during EM was evidenced by a two-fold increase in radius of curvature of the septal segment normalized for LV area (.57 ± .02 to .94 ± .06 U, $P < .001$). Simultaneously, LV ED areas decreased from control to EM on cross-section (19.1 ± 1.1 to 15.7 ± .7 cm^2, $P < .005$) and longitudinal views (29.8 ± 2.1 to 20.7 ± 1.5 cm^2, $P < .001$) without a significant change in end systolic area. RV ED diameter increased from control to EM (1.1 ± .1 to 1.5 ± .2 cm, $P < .005$). Thus, the normal septum is a highly movable structure influenced by acute RV volume changes. Other events which change RV loading conditions may have significant effects on the LV by displacing the septum.

IMPAIRED RATE OF LEFT VENTRICULAR RELAXATION IN PATIENTS WITH CORONARY ARTERY DISEASE AND LEFT VENTRICULAR DYSFUNCTION.

Silvio E. Papapietro, M.D., William J. Rogers, M.D., FACC, H. Cecil Coghlan, M.D., Richard O. Russell, Jr., M.D., FACC, Dimitry Zissermann, Ph.D., Charles E. Rackley, M.D., FACC, Univ of Ala, Birmingham, Ala.

It has been suggested that the rate of left ventricular (LV) relaxation is related to the inotropic state, end systolic fiber length and peak developed pressure, but there is little information available regarding the rate of LV relaxation in patients (pts) with coronary artery disease (CAD) and LV dysfunction. In order to assess the rate of LV relaxation, high fidelity LV pressure measurements were obtained with manometer tip catheters in 40 pts and the signal was analyzed by a digital computer to yield the maximal rate of pressure rise (Pos dP/dt) and the maximal rate of pressure fall (Neg dP/dt). Selective coronary arteriography and biplane LV angiography with determination of LV volumes, ejection fraction (EF) and percent abnormally contracting segment (ACS) (when present) were performed in all pts. In 10 pts with normal LV function ($EF > 0.50$, no asynergy) mean Neg dP/dt (2074 ±121 mmHg/sec) was significantly ($P=0.008$) greater than in 30 pts with CAD and LV dysfunction (1706 ± 65 mmHg/sec). In 9 pts with LV dysfunction and $EF < 0.35$ mean Neg dP/dt was reduced to 1405 ± 107 mmHg/sec, significantly ($P=0.0009$) lower than in pts with normal LV function. Neg dP/dt correlated well with EF ($r=0.75$), with Pos dP/dt ($r=0.75$) and with ACS ($r=-0.74$), correlated less well with LV end-systolic volume ($r=-0.63$) but did not correlate with LV peak developed pressure ($r=0.07$).

These data suggest that the rate of LV relaxation, as assessed by Neg dP/dt, 1) Is impaired in pts with CAD and LV dysfunction, and the extent of impairment is related to the severity of the dysfunction as determined angiographically by EF and ACS, 2) In these pts the rate of LV relaxation is inversely related to LV end-systolic volume, and, 3) Is not related to peak LV developed pressure.

REGIONAL PRESSURE DIFFERENCES IN THE LEFT VENTRICLE

H.L. Falsetti, MD, FACC; M.S. Verani, MD; C.J. Chen, PhD with the Technical Assistance of J.A. Cramer and R.A. Lenth, CV Center and CV Div, Depts of Int Med and Engineering, Univ of Iowa and VA Hospitals, Iowa City, IA

Theoretically, pressure should be distributed in the left ventricle (LV) as a function of both space and time if blood is to have directional flow.

Regional pressure differences (RPD) were examined in the LV of 20 open-chested dogs. High fidelity transducers were implanted through stab wounds at 3 positions in the LV: the base (B), equator (EQ) and apex (APX). Simultaneous, high fidelity LV pressures were compared in each region under rest conditions and during graded infusions of isoproterenol (ISP) and propranolol (PROP). In the baseline condition there were slight but significant differences between the APX and B in end-diastolic pressure, peak systolic pressure (PSP), peak DP/DT and Vmax. At rest, the largest RPD in PSP was 9 mmHg (mean=1.8±3.6) and the largest during diastole was 5 mmHg (mean=1.3±2.1). During ISP infusion the RPD in PSP were accentuated; the largest seen was 84 mmHg between APX and B (mean=20±23 mmHg). Vmax became 45% higher at B than at APX. PROP decreased these RPD.

These results indicate that there are RPD in the LV cavity, with the highest pressures decreasing sequentially from the apex to the equator and to the base. These RPD affect all derived pressure indices and these changes can be increased or decreased by drug intervention. Thus, the position of catheters in the LV cavity is important when pressure-dependent LV parameters are compared in different conditions.

LIMITATIONS OF POST-EXTRASYSTOLIC POTENTIATION (PEP) IN PREDICTING MYOCARDIAL VIABILITY DURING ACUTE ISCHEMIA
Henry G. Hanley, MD, Thomas Patrick, James S. Cole, MD, FACC, and William O'Connor, MD, VA Hospital, Wenner-Gren Lab, and Univ. of Ky., Col. of Med., Lexington, Kentucky

PEP has been suggested to be of value in identifying ischemic but viable myocardium whose function may be improved by coronary artery bypass surgery. To evaluate this, 10 dogs were instrumented with left circumflex coronary artery (LCCA) flow probes and occluders, pacing wires, left ventricular pressure (LVP) gauges and ultrasonic segment length gauges placed near the LCCA. The dogs were studied in the conscious, chronically instrumented state following recovery from surgery. 1 hour LCCA occlusions followed by reperfusion (4 days) were studied. During LCCA occlusion timed premature ventricular contractions (PVC's) (n=411) were induced and PEP measured. LCCA occlusion decreased LVP (133/6 to 117/7 mmHg) ($p<.001$) (Student t test) and LV dp/dt (3240 to 2698 mm/sec) ($p<.001$). Both diastolic (10.00 to 10.20mm) ($p<.001$) and systolic (9.07 to 9.77 mm) ($p<.001$) segment lengths increased and segment shortening decreased markedly (0.96 to 0.44 mm) ($p<.001$) (all 15 segments). In the hypokinetic segments (n=9), PEP increased ischemic shortening (0.74 to 0.89) ($p<.05$). However shortening did not occur in segments (n=6) that were akinetic or dyskinetic (-.29 to -.33 mm) ($p<.4$). On reperfusion all segments showed improvement in shortening and at histological examination after sacrifice all segments were found to be in areas of viable myocardium. These results demonstrate that when acute ischemia is severe enough to produce akinesis or dyskinesis PEP is not useful in predicting myocardial viability. When these conditions are present in the clinical setting caution should be utilized in the interpretation of PEP data.

TUESDAY, MARCH 7, 1978
AM
BASIC SCIENCE INVESTIGATION—I
8:30 to 12:00

EPICARDIAL VASODILATOR RESERVE IN THE PRESENCE OF "CRITICAL STENOSIS". Kim P. Gallagher, MS, John D. Folts, Ph.D., Ronald Shebuski, BS, George G. Rowe, M.D. FACC, Dept. Med., Univ. Wisc., Madison, WI. 53706.

Coronary "critical stenosis" is the term used to describe partial obstruction which eliminates reactive hyperemia (presumably because downstream arterioles have dilated maximally to compensate for a proximal stenosis). Evidence of distal vasomotor capacity exists, however, despite the presence of severe constriction. Coronary blood flow (CBF) in the circumflex (LCC) artery and blood pressure in the aorta and distal LCC was studied in 6, open chest, anesthetized dogs. The LCC artery was obstructed sufficiently to eliminate 95-98% of reactive hyperemia but maintain resting blood flow. The regional distribution of myocardial blood flow (MBF) was studied with tracer microspheres (15 μ diameter) before and after intracoronary (in distal LCC catheter) administration of adenosine (ADEN, 5 μM). The inner (I) to outer (O) ratio of flow in the obstructed bed was not changed by the stenosis (I/O = 1.27 ± .04 to I/O = 1.29 ± .04, NS). ADEN decreased I flow from 1.00 ± .04 ml/min/g to 0.75 ± .04 ml/min/g ($p<.001$) and increased O flow from 0.77 ± .02 ml/min/g to 1.28 ± .06 ml/min/g ($p<.001$). The I/O ratio decreased from 1.29 ± .04 to 0.65 ± .04 ($p<.001$). Simultaneously measured LCC CBF (by electomagnetic flowprobe) increased from 29 ± 2 ml/min to 36 ± 2 ml/min ($p<.01$). Thus, arteriolar vasodilator reserve persists in the presence of severe proximal stenosis but the vasomotor capacity is limited to O layers of myocardium and shunting of flow from I to O layers can occur.

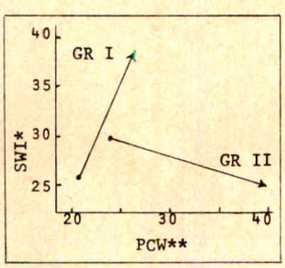
DETECTION OF FUNCTIONAL VENTRICULAR RESERVE BY EXERCISE HEMODYNAMICS IN PATIENTS WITH SEVERE CONGESTIVE HEART FAILURE. **Harris Gelberg MD; Stanley Rubin MD; Bruce Brundage MD, FACC; William Parmley MD, FACC; Kanu Chatterjee MD, FACC; University of California, San Francisco, CA.**

Eighteen patients on digoxin and diuretics in Class 3 or 4 congestive heart failure were exercised in recumbency, using a bicycle ergometer with a Swan-Ganz thermodilution catheter in the pulmonary artery position. Two groups were identified by their response to symptom limited maximum exercise. Group I showed modest increases in pulmonary capillary wedge pressure with an increase in stroke work index while Group II showed substantial increase in pulmonary capillary wedge pressure with little change in stroke work index (see graph).

	Δ PCW	Δ SWI	ΔCardiac Output	ΔHeart Rate	ΔMean Arterial Pressure
GR I Mean	5.0	12.0	1.7	17.6	13.6
N= 6 ± SEM	2.2	1.6	0.4	6.2	7.2
GR II Mean	16.8	- 4.6	0.8	36.3	13.5
N=12 ± SEM	2.6	2.4	0.2	3.6	2.4

Mean maximum workload was 191 kilopond/minute in Group I and 167 kilopond/minute in Group II.

Conclusion: Despite similar history, congestive heart failure class and resting hemodynamics, there is a difference in ventricular reserve in response to exercise in these groups. Exercise hemodynamics may be an important test in evaluating the status of patients in congestive heart failure.



* gm·m/m²
** mm Hg

TRANSMURAL DIFFERENCES IN MYOCARDIAL PERFUSION RELATED TO PRELOAD. Avery K. Ellis, MD; Francis J. Klocke, MD, FACC, State Univ. of N. Y. at Buffalo, Buffalo, N. Y.

The effect of preload on the transmural distribution of myocardial blood flow is controversial. The left circumflex artery [LCA] was cannulated and perfused from the left subclavian artery in 7 open-chest dogs. An in-line solenoid, triggered by the R-wave of the ECG, was adjusted so that perfusion, monitored by an in-line flowmeter, occurred only during diastole. Autoregulation was abolished by maximal vasodilation with Chromonar (5 mg/kg). Under these conditions, any differences in local myocardial blood flow measured by radioactive microspheres are presumably due to local differences in diastolic resistance.

Measurements were made at normal preload (mean left atrial pressure [MAP] = 5 ± 1.0 [SEM] mm Hg) and at increased preload (MAP = 20 ± 2.0 mm Hg). Despite diastolic perfusion and a significant pressure drop across the perfusion circuit at high flow velocities, overall microsphere flow in the LCA distribution was 1.55 ± 0.16 cc/min/g at normal preload and 1.45 ± 0.14 cc/min/g at increased preload. The ratio of endocardial flow to epicardial flow decreased from 0.76 ± 0.05 at normal preload to 0.54 ± 0.02 at increased preload ($p < 0.01$). The LCA pressure at which inflow ceased [Pc], determined by stepwise constriction of the perfusion circuit, was 14 ± 1.7 mm Hg at normal preload and increased to 22 ± 1.2 mm Hg at elevated preload ($p < 0.01$). Local diastolic resistance was calculated as the quotient of driving pressure and local flow, with driving pressure taken as the difference between downstream LCA pressure and Pc. With increasing preload, subepicardial resistance remained constant while subendocardial resistance increased significantly.

We conclude that small differences in transmural resistance, present at normal preload, are accentuated with increasing preload.

RELATIVE ROLES OF CORONARY ATHEROSCLEROSIS AND MYOPATHY IN CARDIAC DISEASE OF DIABETES

Bunyad Haider, MD, FACC; Chien-Kuo Yeh, PhD; George Thomas, MD; Won-Kyu Lee, MD; Henry A. Oldewurtel; Michael M. Lyons, MD; Timothy J. Regan, MD, FACC, CMDNJ-New Jersey Medical School, Newark, NJ.

The relative contributions of coronary occlusive processes and myopathy to cardiac disease in diabetes mellitus is in dispute. To examine this question, two groups of young adult male rhesus monkeys were fed a diet with 40% of calories as lipid and 0.8% cholesterol. Nine were made diabetic (D) with sequential low doses of alloxan. Fasting serum glucose was 273±22 mg%. Serum cholesterol rose threefold in both groups. After 18 mos. animals were studied by indicator dilution in the intact anesthetized state at similar levels of heart rate, aortic pressure and heart weight. During infusion of saline in 9 controls (C) left ventricular end-diastolic pressure (EDP) rose from 10.7±0.7 mmHg to 15.9±1.3. The rise in D from 11.7±1.7 to 26.2±2.7 was significantly greater than C ($P<.005$), despite similar stroke volume increments. Left ventricular end-diastolic volume (EDV) in D, did not change significantly, while EDV rose 53% ($P<.005$) in C. Collagen increased to 54.7±2 µg/mg in D versus 39.7±2 in C ($P<.001$) and localized to interstitium by microscopy was apparent basis for diminished compliance. Atrial pacing was not associated with significant electrocardiographic changes, lactate production or differences in coronary blood flow by the ^{85}Kr technique. Coronary arteries showed lipid streaks and flat plaques in both groups without obstructive lesions. Thus, in a species susceptable to atherosclerosis, the diabetes alters myocardial compliance and composition before the appearance of obstructive atherosclerosis.

IMPAIRED MYOCARDIAL PERFORMANCE AND RESPONSE TO CALCIUM IN EXPERIMENTAL ALCOHOLIC CARDIOMYOPATHY

Masaya Kino, MD; Kathryn A. Thorp; Oscar H.L. Bing, MD and Walter H. Abelmann, MD, FACC. Dept. of Medicine, Harvard Medical School and Beth Israel Hospital, Boston, MA.

Unlike acute administration, chronic feeding of ethanol has not been shown to consistently depress myocardial function. We used the isolated heart muscle preparation to permit detection of early mechanical changes not apparent from the assessment of intact hemodynamics.

Ethanol, comprising 36% of dietary calories was administered to Sprague-Dawley rats for 5 weeks. In a pairfed group, ethanol was replaced isocalorically with sucrose. Isolated left ventricular muscle preparations were studied in Krebs-Henseleit solution while stimulated 12 times/min at 28°C. Changes in developed tension (T), g/mm^2 are summarized:

	Calcium mM/L			
	1.25	2.5	5	7.5
Pairfed (n=8)	6.6±0.8*	7.8±0.9	7.9±0.9	7.5±0.9
Ethanol (n=8)	5.2±0.4	5.8±0.4	5.9±0.4	5.8±0.4

*Means±SEM

Three way analysis of variance of the effects of ethanol at calcium concentration of 1.25, 2.5, 5.0 and 7.5 mM/L revealed a significant decrease ($p<0.01$) from pairfed in T (20%), dT/dt (17%), and -dT/dt (12%). Furthermore, there was significantly less ($p<0.05$) augmentation of T, and dT/dt by increasing calcium from 1.25 to 2.5 mM in ethanol fed rats.

Thus, ethanol administered chronically to rats is associated with depressed performance of isolated heart muscle as well as a decreased sensitivity to calcium.

COMPARISON OF EFFECTS OF ACUTE CORONARY OCCLUSION IN ACUTELY AND CHRONICALLY DENERVATED CANINE HEARTS

John X. Thomas, Jr., PhD; Carl E. Jones, PhD; David E. Euler, BA; Walter C. Randall, PhD, FACC, Loyola University Stritch School of Medicine, Maywood, Illinois

Recent evidence suggests chronic surgical cardiac denervation provides protection against loss of contractile force with myocardial ischemia. This study determined 1) if acute and chronic cardiac denervation provided the same degree of protection, and 2) if infarct size was reduced in either group. Three groups of dogs were used; 10 acutely denervated (AD) in which thoracic vagi and stellate ganglia were cut and α and β blockades were maintained with phentolamine (1.25mg/kg.) and propranolol (1mg/kg.), 12 chronically denervated (CD) in which all intrapericardial nerves were cut 2 wks. prior, and 10 non-denervated (ND) dogs. In all animals the LAD was ligated above the apical branch. No significant change in systemic arterial pressure was noted and none of the animals succumbed to failure or fibrillation during the occlusion. Contractile force in the ischemic area measured with strain gauge arches fell by 83±7.6% of control in AD, but decreased by only 21.5±6.59% of control in CD. After 5 hrs. of occlusion the infarct was delineated in sections of left ventricle (LV) using nitro-blue tetrazolium strain for dehydrogenases. The infarct was cut from the sections, weighed, and expressed as % LV weight. Mean LV weights in AD, ND and CD were 99.3, 80.4 and 81.9gm. respectively. Mean infarct sizes in AD and ND were 16.2 and 20.1% respectively ($p<.05$), while infarct size in CD was only 3.8% ($p<0.001$). These results suggest that chronic cardiac denervation provides a greater reduction in ischemic injury produced by acute coronary occlusion than acute denervation. This effect may result from alterations in myocardial blood flow or metabolism in the chronically denervated heart.

CORONARY COLLATERALS: DEVELOPMENT AND FUNCTIONAL SIGNIFICANCE

Willem Flameng, M.D., Franz Schwarz, M.D., and Wolfgang Schaper, M.D., Kerckhoff-Institut, D-635 Bad Nauheim

The development and functional significance of coronary collaterals was studied using the tracer microsphere technique in 18 out of 25 mongrel dogs surviving complete chronic occlusion of the left circumflex coronary artery (LC). In a first group of 8 dogs resistance of the preexistent collaterals was determined during short acute occlusion of the LC. The mean value was 8.49 resistance units (R.U.). Six weeks after the implantation of an ameroid constrictor on the LC collateral resistance decreased significantly ($p<0.005$) to 0.27 R.U.. Two dogs of this group developed a transmural and one a subendocardial infarction after chronic LC-occlusion. Aorto-coronary bypass grafting restored regional coronary reserve completely in dogs without and partially in dogs with infarction. In the second group of 10 animals no myocardial infarction was found 6 weeks after chronic LC-occlusion. In this group stress was performed by intravenous infusion of norepinephrine. In the areas perfused by normal coronary arteries there was a significant increase of subepicardial (epi) and subendocardial (endo) blood flow (MBF) with increasing pressure-rate product (PRP): epi $r = 0.56$, $p<0.005$ and endo $r = 0.68$, $P<0.01$. The collateralized endo, however, failed to rise its MBF with increasing PRP ($r=0.23$, $p>0.05$). After bypass to the occluded LC the normal MBF-PRP-relation was restored. Thus, a significant collateral circulation develops after chronic coronary obstruction and protects the myocardium against infarction in most cases. The functional capacity of collaterals, however, is limited and becomes inadequate under stress conditions.

RESTORATION OF INWARD SLOW CURRENT IN HYPOXIC HEART MUSCLE BY ALKALINE pH

Luiz Belardinelli, MD, Stephen M. Vogel, BS, Nick Sperelakis, PhD, Rafael Rubio, PhD, Robert M. Berne, MD, University of Virginia, Charlottesville, Virginia.

Hypoxia and agents that deplete the cellular ATP level (e.g., cyanide) depress the slow inward current in heart muscle. Acid pH accelerates the rate of decay of the contractions of hypoxic ventricular muscle whereas alkaline pH slows it. This potentiating effect of acid pH on the rate of blockade may be due to an effect on the inward slow Ca^{++} current that enters during the plateau of the action potential. Therefore, we determined the rate of inhibition of the slow current at normal, acid and alkaline pH levels (7.4, 6.8 and 8.0) during hypoxia in isolated guinea pig papillary muscle. The fast Na^{+} channels were voltage-inactivated by partial depolarization with an elevated (25 mM) K^{+} solution. Adding isoproterenol (10^{-6} M) resulted in a slowly-rising overshooting Ca^{++}-dependent action potential (the "slow response") upon electrical stimulation. In normoxia, pH changes to 6.8 or 8.0 had no significant effect on the slow response as assessed by the maximal upstroke velocity ($+\dot{V}_{max}$). In contrast, the time course of blockade during hypoxia was markedly pH-dependent. During hypoxia, the time for 50% reduction of $+\dot{V}_{max}$) was a function of pH: 30 min (pH 8.0), 15 min (pH 7.4), and 9 min (pH 6.8). Moreover, after complete blockade of the slow response at pH 6.8 during hypoxia, changing the pH to 8.0 almost immediately restored the slow response (>50% of the initial value) which persisted for 20-60 min. Similar results were obtained with the action potential plateau. The results demonstrate that the slow Ca^{++} current in myocardial cells only gradually declines with hypoxia in alkaline pH.

SELECTIVE INHIBITION OF DELAYED RECTIFYING POTASSIUM CURRENT IN CARDIAC PURKINJE FIBERS BY TETRAETHYLAMMONIUM ION

Sukenobu Ito, MD; Borys Surawicz, MD, FACC, University of Kentucky Medical Center, Lexington, Ky.

The different postulated components of K^{+} conductance (gK) in cardiac membrane include: 1) steady state background current i_{K1}, 2) pacemaker current i_{K2}, and 3) delayed rectifying current i_X. It is not clear whether they are independent from each other. We studied the effects of intracellularly applied tetraethylammonium ion (TEA) in canine Purkinje fibers. TEA prolonged action potential duration (APD) at rates from 0.1 to 3.0Hz (average 87.2% at 1.0Hz), and increased the number of beats required to reach steady state APD after changes from quiescence to 0.1Hz (18.5 $\pm$ 8 vs 28.1 $\pm$ 6*), from 0.1Hz to 0.25Hz (16.5 $\pm$ 6 vs 25.1 $\pm$ 7*), and from 0.25Hz to 0.5Hz (12.3 $\pm$ 4 vs 20.3 $\pm$ 6**) (aver. $\pm$ S.D.,n=10). This indicates that TEA blocks K^{+} channel responsible for determining APD (i_X). However, intracellular TEA did not change: 1) slope of diastolic depolarization, and 2) maximum diastolic potential (MDP) at extracellular K^{+} concentrations $[K^{+}]_o$: 5.4, 8.1, and 10.8mM/L. This indicates that the components of gK responsible for maintenance of MDP and phase 4 (i_{K1} and i_{K2}) are not sensitive to TEA. We concluded that: 1) within the range of $[K^{+}]_o$ from 5.4 to 10.8mM/L, K^{+} currents responsible for MDP and pacemaker activity, i.e. background current i_{K1} and i_{K2} are insensitive to TEA, while the delayed rectifying K^{+} current i_X regulating APD is selectively inhibited by TEA, 2) TEA action supports the concept of several independent K^{+} channels in cardiac membrane.

*$p<0.05$, **$p<0.01$

ELECTROPHYSIOLOGIC INTERACTIONS BETWEEN ACUTE ISCHEMIA AND HEALED EXPERIMENTAL MYOCARDIAL INFARCTIONS IN CATS

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Myocardial infarctions were created in 3 groups of cats by distal ligation of the left coronary system. All were monitored for arrhythmias, followed by study of the isolated left ventricle (LV) in tissue bath. Group 1 = 8 acute myocardial infarction (AMI) cats sacrificed at 30-120/min. Unifocal PVCs occurred in 5, and transient ventricular tachycardia (VT) in 2. Group 2 = 24 healed MI cats (HMI) studied 2-4 months after AMI. Six had chronic ventricular ectopic activity (VEA), ranging from single PVCs to short runs of VT. Group 3 = 8 cats (AMI-HMI) in which a second AMI was created adjacent to an HMI. In contrast to AMI cats, acute arrhythmias in the AMI-HMI group included chaotic VEA in 5 of 8, leading to VT in 2 and VF in 3. During tissue bath studies in the AMI group, sustained ventricular activity (SVA) could not be initiated by premature stimulation (PS) of LV endocardium. In 8 of 24 HMI cats, SVA in tissue bath was initiated by PS of surviving endocardium over the HMI. In Group 3 (AMI-HMI), SVA (5 of 8 cats) resulted from PS over the AMI, and less uniformly over surviving HMI tissue. SVA was triggered in AMI-HMI LV's by PS in 4 of 5 cats with spontaneous VEA on ECG. Endocardial mapping studies suggested that the triggered SVA resulted from reentry involving infarcted and normal tissue. PS initiated SVA most predictably in sites having short local refractory periods (LRP) in hearts with markedly disparate LRP durations. We suggest that, in this model, the potentially lethal spontaneous VEA correlated best with the coexistence of AMI and HMI tissues. This may be explained by interaction of differing electrophysiologic properties of acutely infarcted, healed infarcted, and normal tissues.

SINO-ATRIAL REENTRY INDUCED BY VAGAL STIMULATION

Joseph F. Spear, Ph.D., F.A.C.C., Margaret B. Alonso, M.S. and E. Neil Moore, D.V.M., Ph.D., F.A.C.C., University of Pennsylvania, Philadelphia, Pennsylvania

Experiments were performed on 12 isolated rabbit sinus node-atrial preparations in which vagal innervation was maintained. The tissues were superfused with Tyrode's solution containing 1.0 mg/L propranolol to eliminate beta adrenergic influences. Standard microelectrodes were used to record transmembrane potentials from pacemaker and perinodal fibers. Bipolar surface electrodes were used to record from the crista terminalis and right atrial appendage. Vagal stimulation (VS) was accomplished by applying brief 100 msec, 100 Hz trains of 4 msec pulses to the superior vena cava by way of close bipolar silver electrodes. Initial slowing of spontaneous automaticity followed VS with a latency of 200 msec. The maximum slowing occurred from 300 to 500 msec and the effects lasted 2 to 10 seconds. In 4 of 12 preparations the slowing of automaticity induced by VS was also accompanied by either concealed or manifest sinus node (SN) reentry 320 to 535 msec following VS. The reentrant activity interacted with automaticity in the SN producing complex but reproducible changes in the pattern of atrial rhythm following VS. These included paradoxical shortening of cycle length to less than control values due to manifest reentry and also abnormal prolongation of cycle lengths due to concealed reentry. Multiple transmembrane potential recordings indicate that VS causes slowing of conduction within the SN. The conduction slowing was most pronounced in the perinodal region. This non-uniform influence on conduction provides the substrate for reentry to occur, and suggests the mechanism by which phasic alterations in vagal tone may contribute to sino-atrial reentry in the intact animal and man.

EFFECT OF CHOLINERGIC STIMULATION ON VULNERABILITY TO VENTRICULAR FIBRILLATION DURING MYOCARDIAL ISCHEMIA AND REPERFUSION

Richard L. Verrier, PhD, FACC; Wesley W. Brooks, MS; Bernard Lown, MD, FACC, Cardiovascular Research Laboratories, Department of Nutrition, Harvard School of Public Health, Boston, Ma.

Vagus nerve stimulation (VNS) has been shown to decrease vulnerability to ventricular fibrillation (VF) in the normal heart but its effect during coronary artery occlusion (CO) remains controversial. We therefore examined the influence of VNS and direct muscarinic receptor stimulation with methacholine (MCh)(5 µg/kg/min, i.v.) on ventricular vulnerability during a 10-minute period of CO and during abrupt reperfusion (R). Thirty-four chloralose-anesthetized dogs with previously implanted balloon catheters around the left anterior descending coronary artery were studied. The VF threshold was assessed using a single 10 msec constant-current stimulus during ventricular pacing (214 beats/min). The following results were obtained (means ± SE). * = p <0.05 and ** = <0.01 when compared to control values.

	VF threshold (ma)			
	Pre-occlusion	Occlusion (min) 2'	Occlusion (min) 8'	Reperfusion
Control	17 ± 2	6 ± 1	8 ± 2	5 ± 1
VNS	33 ± 4*	18 ± 4*	23 ± 5**	3 ± 1
MCh	22 ± 2*	10 ± 2	18 ± 3**	6 ± 1

These results indicate that VNS or muscarinic receptor stimulation by MCh affords partial protection against VF during coronary artery occlusion, but is ineffective during reperfusion. These findings indicate, moreover, that CO and R are mediated by different mechanisms.

LYSOPHOSPHOLIPIDS: POTENTIAL PRECIPITANTS OF MALIGNANT ARRHYTHMIA DUE TO ISCHEMIA

Peter B. Corr, PhD; Francis X. Witkowski, MS; David A. Price; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri

Accumulation in ischemic myocardium of lysophospholipids, catabolites of phospholipids with detergent properties, has recently been reported from our laboratory. To determine whether these compounds are arrhythmogenic, isolated canine Purkinje fibers were perfused at 5.2 ml/min with oxygenated Krebs buffer, 5 mM glucose, and equimolar albumin and palmitate (0.4 mM) with or without 1.5 mg/ml of albumin-bound lysophosphatidyl choline (LPC) (corresponding to levels found in ischemic myocardium). Albumin ± palmitate did not alter electrophysiological parameters based on computer-analysis of continuous, intracellular recordings including: resting potential (-95 ± 3 mV (SD)), peak dV/dt (1017 ± 97 V/sec), phase 0 overshoot (42 ± 3 mV), or action potential duration (253 ± 18, 271 ± 17, and 313 ± 18 msec at 50, 70, and 95% recovery). In contrast, LPC fractionated the action potential; markedly decreased resting potential by 42 ± 6% (SE), peak dV/dt by 72 ± 9, overshoot by 77 ± 19, and duration by 52 ± 8, 37 ± 8, and 25 ± 10; and completely inhibited both spontaneous and electrically stimulated depolarization. During subsequent perfusion without LPC, automaticity increased dramatically to 237% of the control rate, while resting potential, peak dV/dt, overshoot and duration recovered only slowly to 89, 46, 86, and 92% of control in 70 minutes. Thus, lysophospholipids in concentrations equivalent to those in ischemic myocardium elicit striking electrophysiological derangements, potentially responsible for malignant arrhythmias due to ischemia.

TUESDAY, MARCH 7, 1978
AM
PHARMACOLOGY OF VASODILATOR AND INOTROPIC AGENTS
8:30 to 12:00

QUANTITATIVE DETERMINATION OF TRINITROGLYCERIN IN HUMAN PLASMA. Jeanne Wei,M.D. and Philip R. Reid, MD, FACC. The Johns Hopkins Medical Institutions. Baltimore, Maryland

Despite its widespread use for over one hundred years,little is known about the bioavailability of trinitroglycerin (TNG)administered by different routes due, in part, to lack of an adequate method for measurement of TNG in blood. We have developed a simple, sensitive and specific method for quantitative measurement of TNG in human plasma using gas-liquid chromatography with electron-capture detection.The procedure involves triple extraction of plasma with hexane and use of dinitrobenzene as an internal standard.This assay provides a linear response over a concentration range of .2 to 60 ng/ml without interference from endogenous nitrates.

We measured the plasma TNG levels in 9 patients In 5 patients, the TNG was given IV as a constant infusion (37.5-200 ug/min)to lower the mean blood pressure by 10 mm Hg. Plasma levels ranged from .4 to 2.7 ng/ml (mean,1.66). In 3 patients receiving 3'' of 2% TNG paste, plasma levels 1 hour after topical application ranged from 1.2 to 3 ng/ml (mean, 2.3). After 600 ug TNG sublingually , the levels were 5.2 ng/ml at 6 min and fell with a half-life of 17.5 min.

These results suggest topical TNG provides plasma levels at 1 hr similar to those produced by IV infusion and the levels after sublingual TNG fall rapidly as would be predicted from the clinical response.This assay may facilitate optimization of nitrate therapy in patients using different routes of administration.

DIRECT INOTROPIC EFFECTS OF THE AFTERLOAD REDUCING AGENTS, HYDRALAZINE AND PRAZOSIN, EVALUATED IN ISOLATED CAT PAPILLARY MUSCLE PREPARATION

Kay Riggs, BS: Dean T. Mason, MD, FACC; Garrett Lee, MD; University of California, Davis, California

The antihypertensive drugs, hydralazine and prazosin, have recently been shown to be of considerable value in the management of patients (pts) with acute and chronic congestive heart failure. Both drugs raise cardiac output by decreasing ventricular impedance via reduction in systemic arteriolar resistance. Prazosin also directly diminishes systemic venous tone, thereby decreasing cardiac preload and relieving pulmonary congestion. However, it is not known whether these two agents possess any direct inotropic effects on the myocardium which would contribute to these beneficial actions. Thus control contractile properties of 12 isolated cat papillary muscles were determined at Lmax utilizing 7 cumulative clinically physiologic meaningful doses of hydralazine (10^{-6} to 3.3 mg) (6 muscles) and prazosin (2×10^{-4} to 0.2 mg) (6 muscles) in a 10 ml bath preparation containing Krebs bicarbonate solution. The following parameters were analyzed: peak tension (T), maximum rate of tension development (dT/dt) and maximal velocity of shortening (Vmax). Prazosin produced no significant changes in peak T, dT/dt and Vmax from control values of 3.75 gm/mm^2, 14.40 gm/sec/mm^2 and 1.21 mm/sec respectively. In contrast, hydralazine caused significant 8% increase in peak tension from control of 3.76 gm/mm^2 ($p<.01$), 12% rise in dT/dt from 15.05 gm/sec/mm^2 ($p<.05$), and 23% elevation in Vmax ($p<.001$). These data indicate that some of the hemodynamic benefit achieved by hydralazine is derived from its positive inotropic action. Since this study documented that prazosin is without direct effect on contractile state, the salutary cardiocirculatory actions of prazosin are due completely to the agent's vasodilator influence on the systemic arterial and venous beds.

COMPARATIVE EVALUATION OF THE EFFICACY OF INTRAVENOUS NITROGLYCERIN AND NITROPRUSSIDE ON REDUCING VENTRICULAR ISCHEMIA MEASURED BY VECTORCARDIOGRAPHIC-ST MAGNITUDE IN EXPERIMENTAL PORCINE MYOCARDIAL INFARCTION

James M. Foerster, MD; Zakauddin Vera, MD; David Janzen, BS; Dean T. Mason, MD, FACC, Univ. of Calif., Davis, Calif.

Controversy remains concerning clinical effects of nitroglycerin (NTG) and nitroprusside (NP) on extent of muscle damage with acute myocardial infarction (AMI). To evaluate influence of these two vasodilators on degree of such muscle injury, vectorcardiographic-ST magnitude rise (STM) was used to estimate myocardial ischemia that occurred with AMI in the intact porcine heart, the coronary circulation of which is similar to man. Previously we have shown the Frank XYZ leads ST sum correlates closely with ST sum of multiple epicardial grid leads. In ten pigs, following thoracotomy and coronary ligature, the chest was closed and Frank XYZ leads obtained. Natural evolution of STM over 4 hours was observed in four animals, and in six pigs NTG and NP dose-responses were obtained following AMI. In pharmacologic treated animals, hemodynamics and STM were recorded 30-60 minutes after coronary ligation (pre-drug control) and then remeasured after either NTG or NP; each animal was used as its own control with time allowed between each drug for return of control hemodynamics.

	Control $\overline{BP}$	Control LVFP	$\overline{BP}$ at Min STM	LVFP at Min STM	Min STM attained
NTG	103	22	76	21	+81%
NP	109	26	82	17	+66%

Min STM = minimum STM rise; $\overline{BP}$ = mean blood pressure (mm Hg); LVFP = left ventricular filling pressure (mm Hg). These data indicate that both NTG and NP ↓ ischemia extent in experimental AMI. Moreover, with ↑ LVFP, NP appears more effective than NTG in ↓ ischemia with AMI.

COMPARATIVE HEMODYNAMICS OF ORAL PRAZOSIN AND HYDRALAZINE IN CHRONIC HEART FAILURE.

Thomas Ports, MD; Kanu Chatterjee, MD, FACC; William Parmley, MD, FACC; Anne Norman, BA: University of California, San Francisco, California.

Vasodilators have an established role in the therapy of heart failure. Recent studies have demonstrated hemodynamic improvement in chronic congestive heart failure with oral hydralazine and most recently oral prazosin. This study compares the hemodynamic effects of hydralazine (HD) and prazosin (PR) in the same patients with chronic heart failure. Changes in heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure, pulmonary capillary wedge pressure (PCW), right atrial pressure, cardiac index (CI), stroke volume index (SVI), stroke work index (SWI), systemic (SVR) and pulmonary vascular resistance were determined in 12 patients after 3, 4 and 5 mg of PR and compared to initial control hemodynamics (C_1). After second control hemodynamics (C_2) the effects of 75 mg oral HD were determined in the same patients. The results were:

	HR	MAP mmHg	PCW mmHg	CI L/min/m^2	SVI ml/m^2	SWI g·m/m^2	SVR*
C_1	86±7	87±3	24±1	2.1±.1	26±2	22±3	1776± 85
PR-5 mg	87±7	79±3	19±2	2.5±.2	30±3	25±3	1410±118
C_2	87±7	87±3	24±1	2.1±.1	25±2	22±2	1760± 86
HD	89±6	79±2	20±1	3.3±.2	38±3	30±2	1045± 60

PR increased CI by 19% and decreased SVR by 21%, while in these patients HD increased CI by 52% and decreased SVR by 41%. There was no change in other hemodynamic parameters with either drug.

Conclusion: These findings suggest that both PR and HD produce beneficial hemodynamic response and within prescribed doses, HD is twice as effective as PR.

* dynes/sec/cm^{-5}

ATTENUATION OF THE CARDIOVASCULAR EFFECTS OF NITROGLYCERIN BY INDOMETHACIN.

Esteban Morcillo, M.D. Bertram Pitt, M.D. and Philip R. Reid, M.D. Johns Hopkins Medical Institutions, Baltimore, Maryland.

An earlier report from this laboratory demonstrated that nitroglycerin (TNG) produced a marked increase in myocardial prostaglandins E release when given as a constant infusion (10ug/kg/min). We have extended these observations to examine the effect of indomethacin (IND) on the heart rate (HR), mean arterial pressure (MAP), mean coronary flow (CF) and mean coronary resistance (CR) dose-response curve (DRC) to TNG. In 15 open-chest anesthetized dogs, TNG was given as an intravenous (IV) bolus injection (N=9) (1 to 32 ug/kg) or as a stepwise infusion (N=6) (10 to 160 ug/kg/min). Following the control DRC, IND was injected IV (5 mg/kg) and 30 minutes later the DRC repeated. In 6 control dogs (3 bolus and 3 stepwise infusion) TNG was given as above except only the IND vehicle was used. Results demonstrated that before IND, TNG, both bolus and infusion, produced a dose related increase on HR and CF, and decrease of MAP and CR. Following IND there was 50-60% attenuation in the MAP, CF and CR response at all dose levels of TNG ($p < .01$) with a right downward shift of the DRC. HR response was higher ($p < .05$) after IND with TNG (160 ug/kg/min). No significant changes in the TNG DRC were observed for any parameter following IND vehicle. The results demonstrate that IND attenuates the cardiovascular response to TNG through a noncompetitive antagonism suggesting that prostaglandins partially mediate the effects of TNG.

DEVELOPMENT OF SYSTEMIC VASODILATOR TOLERANCE TO PRAZOSIN WITH CHRONIC USE OF THE AGENT IN AMBULATORY THERAPY OF SEVERE CONGESTIVE HEART FAILURE

Najam A. Awan, MD, FACC; Richard R. Miller, MD, FACC: Kevin S. Maxwell, BS; Dean T. Mason, MD, FACC, University of California, Davis, California

To evaluate whether long-term administration of the new oral vasodilator prazosin (PZ) in the ambulatory therapy of chronic congestive heart failure (CHF) results in gradual attenuation of its marked peripheral circulatory relaxing actions with attendant decrease in the initial dramatic improvement of cardiac performance produced by the drug, in 6 patients with CHF the effects of PZ (40-50 µg/kg) were evaluated by forearm plethysmography prior to initiation of chronic PZ therapy (Study I) and repeated 7 months (6-10 months) after chronic outpatient therapy (Study II). HR = heart rate, beats/minute; $\overline{BP}$ = mean systemic blood pressure, mm Hg; FVT = forearm venous tone, mm Hg/ml; FVR = forearm vascular resistance, mm Hg/ml/100 gm/min; FBF = forearm blood flow, ml/100 g/min. Study I vs II: * = $p < 0.05$, ** = $p < 0.01$, † = $p < .001$, NC = $p > .05$.

	HR	$\overline{BP}$	FVT	FVR	FBF
Study I	NC	↓18	↓62	↓25	↑32
Study II	NC	↑1†	↑10*	↓40**	↓23*

Thus over 7 month period these CHF patients studied developed tolerance to PZ systemic arteriol and venous relaxing effects concomitant with less clinical dyspnea and fatigue relief. However, by ↑ PZ dose, BP reduction reoccurred and symptomatic benefit was regained. Thus chronic cardiac unloading therapy in heart failure with PZ appears to be accompanied by tolerance to peripheral vasodilation. This untoward phenomenon may be overcome by increased prazosin dosage or by temporary change to ambulatory regimen of hydralazine with nitrates.

ANTIBODY REVERSAL OF DIGOXIN-INDUCED INHIBITION OF MYOCARDIAL MONOVALENT CATION ACTIVE TRANSPORT

Thomas J. Hougen, MD, Brian L. Lloyd, MD, MRACP, and Thomas W. Smith, MD, FACC, Peter Bent Brigham Hospital, Boston, Massachusetts

Although digitalis toxicity remains an important clinical problem, the cellular basis for toxicity is not fully known. Digitalis inhibition of the monovalent cation transport enzyme NaK-ATPase has been implicated as a possible mechanism, but it is not known if reversal of toxicity is accompanied by enzyme reactivation or restoration of transport function. We studied the relationship between the appearance of digoxin-induced cardiac arrhythmias and myocardial active transport of the K^+ analog $^{86}Rb^+$ in 33 pentobarbital-anesthetized dogs given vehicle or digoxin (0.3 mg/kg, IV). Transport was also assessed after reversal of arrhythmia by digoxin-specific antibody. Left ventricular samples from control animals given vehicle (n=9) had $^{86}Rb^+$ active uptake of 0.118±0.008 (SEM) nmol $^{86}Rb^+$/mg wet weight tissue/15 min. At onset of ventricular tachycardia (VT), active transport was reduced to 41±3 (SEM)% of control (n=5, $p<0.001$). At onset of fatal ventricular fibrillation, active transport was 20±4% of control (n=5, $p<0.001$). An antibody reversal group (n=5) received digoxin-specific antibody at toxicity (all VT) and reverted to sinus rhythm an average of 74.4±9.4 min later. Active transport at return of sinus rhythm was 51±4% of control. Another group (n=9) given antibody at toxicity returned to sinus rhythm and was allowed to recover. Active uptake of $^{86}Rb^+$ had returned to 92±3% of control values (NS compared to control) 24 hours later. Thus, toxic and fatal digoxin-induced arrhythmias are associated with marked inhibition of myocardial monovalent cation active transport. Otherwise lethal digoxin toxicity is reversed by specific antibody, with concomitant reversal of transport inhibition.

INFLUENCE OF MANNITOL ON ISOLATED CORONARY AND PERIPHERAL ARTERIAL SMOOTH MUSCLE

V.S.R. Krishnamurty, PhD; Richard Adams, PhD; Gordon H. Templeton, PhD; James T. Willerson, MD, FACC, University of Texas Health Science Center, Dallas, Tx.

Our previous studies indicated that hyperosmotic mannitol (M) inhibits vasoconstrictor responses to norepinephrine (NE) and potassium chloride (KCL) in rabbit ear (RE) and cat mesenteric arteries. The mechanism of vasodilation by M (50 mOsm) seemed to be different from that of other well studied vasodilators (Krishnamurty et al, Am J Physiol 232:H59, 1977). In order to further characterize the influence of M (50 mOsm) on contractile activity of vascular smooth muscle, experiments were done using perfused, isolated RE and canine coronary arteries (CCA). Infusion of M to arteries exposed to K^+ (60 mM) caused a consistent vasodilation which lasted approximately 1 hr in CCA and only 30 min in RE artery. The vasodilator response to M was unaffected by other vasodilators; however, the vasodilator effects of several agonists were inhibited by M. Withdrawal of M from the media caused vasoconstriction with elevations in perfusion pressure to levels higher than pre-M values. This vasoconstriction was not prevented by either α or β adrenergic blockade. Intra or extra luminal administration of NE to RE ear artery caused vasoconstriction whereas K^+ caused pressor responses only when administered intraluminally. The pressor responses to NE and K^+ were inhibited by M only when M and the agonist were on the same side of the arterial wall. These findings demonstrate that the vasodilator effect of M in isolated arteries lasts 30 min to 1 hr but indicate that M paradoxically inhibits both contractile and vasodilator responses to various agonists in isolated canine coronary and RE arteries. Abrupt removal of M from the perfusion media produces marked vasoconstriction not prevented by α or β adrenergic blockade in isolated canine coronary arteries.

A DIGOXIN/QUINIDINE ADVERSE DRUG INTERACTION

James A. Reiffel, M.D., FACC, Edward B. Leahey, M.D., Ronald E. Drusin, M.D., FACC, Robert H. Heissenbuttel, M.D., and William P. Lovejoy, M.D., Columbia University, New York, N.Y.

To determine the frequency of an adverse drug interaction between digoxin (D) and quinidine (Q) which we previously discovered incidentally, 26 patients (pts) were evaluated. All pts had serum D levels determined while on steady state doses of D before and during Q therapy (Qsulfate 200-400 mg q6h or Qgluconate 324-648 mg q8h). The D dose during Q was unchanged in 16 pts and decreased in 9 pts as compared to before Q. Serum D levels increased significantly in 23/25 pts during Q therapy. Before Q: mean D level was 1.4 nm/L (range 0.4-3.7) and mean daily D dose was 0.31 mg (range 0.125-0.5). During Q mean D level was 3.2 nm/L (range 1.2-6.4) although mean daily D dose was 0.25 mg (range 0.125-0.5). Pts with changes in BUN or serum creatinine during therapy or with any additional antiarrhythmic drug were not included in this study. New anorexia or nausea appeared in 16/25 pts during Q and disappeared in 10/10 upon holding or reducing D. Of 12 pts without prior VPDs, 3 developed new VPDs after starting Q; 2 of these 3 had ventricular fibrillation or sudden death within 5 days of starting Q. We conclude that giving Q to digitalized pts will induce increases in D levels in most pts. Adverse symptoms and/or serious ventricular arrhythmias following Q may reflect D toxicity rather than Q intolerance and may subside upon withholding D. When starting Q, D doses should be decreased and serum D levels followed.

ALTERATIONS OF CARDIAC MUSCLE INOTROPIC RESPONSIVENESS BY RYANODINE

John L. Sutko, PhD; James T. Willerson, MD, FACC; Henry R. Besch, Jr, PhD, FACC; Larry R. Jones, PhD, MD; Starr Wheelan, BA; August M. Watanabe, MD, FACC, University of Texas Health Science Center, Dallas, Tx.

We have investigated the myocardial effects of ryanodine (R), a drug reported to alter sarcoplasmic reticular (SR) Ca^{2+} movements, in order to assess contributions made by the SR to several inotropic events. Canine and feline right ventricular papillary muscles responded biphasically to increasing concentrations of R, with an initial negative inotropic effect (5nM-1μM), and a subsequent increase in developed force (10-100μM). This response pattern was observed in both normal buffer and in that containing 22 mM K^+ (isoproterenol or dibutyryl cAMP restoration). R (>0.1μM) abolished the increase in the rate of force development normally resulting from paired electrical stimulation and shifted the potentiation from the first (regular) to the second (premature) contraction. The increased contractile force produced by hyperosmolality (50 mOsm mannitol) was also abolished by R (1μM), whereas that due to a doubling of the stimulation rate (0.2 to 0.4 Hz) was unaffected. In the presence of 3.2 mM Ca^{2+}, R (1μM) attenuated the loss of tension observed with decreasing stimulation rates, an effect enhanced by the removal of Mg^{2+}. The observed contractile alterations may in part be due to a diminishment of SR Ca^{2+} release by R, since we have observed R (100μM) to decrease Ca^{2+} efflux in a cardiac muscle membrane fraction enriched with SR, while ATP hydrolysis in this fraction, when measured in the presence of A23187, was not changed. Hence R may provide a new probe for the study of cardiac muscle excitation-contraction coupling.

DOBUTAMINE AND DOPAMINE--COMPARATIVE CARDIOVASCULAR EFFECTS OF MAINTENANCE DOSES IN SEVERE CARDIAC FAILURE. Carl V. Leier, MD; Paul Heban, MD; Pat Huss, RN; Charles A. Bush, MD; Richard P. Lewis, MD, FACC, Ohio State University, Columbus, Ohio.

Twelve patients with end-stage congestive cardiomyopathy underwent a single crossover study of dobutamine (Db) and dopamine (Dp)—24 hr IV infusion each—in order to compare their cardiovascular properties. Based on heart rate response (< 20% increase over baseline) and ventricular irritability (< 12 PVC's/min), the mean maintenance doses of Db and Dp were determined to be 7.1 and 4.0 mcg/kg/min. respectively. Measurements during control (C) and infusion periods included cardiac index (CI), left ventricular filling pressure (LVFP), mean arterial pressure (MAP) and total systemic resistance (TSR). Upper extremity blood flow (UEF) by venous phlethysmography, hepatic blood flow (HBF) by indocyanine green clearance and renal blood flow (RBF) by PAH clearance were performed on 6 of the patients.

Results:		C	Db	C	Dp
CI	L/M^2/min	2.43+.2	3.09±1†	2.49±.2	2.76±.2
LVFP	mmHg	19±2	18±2	18±2	20±2
MAP	mmHg	79±3	83±4	79±3	88±4Φ
TSR	units	19±6	15±3*	19±2	19±1
UEF	ml/100ml/min	3.9±1.1	4.8±9*	3.5±.2	4.2±.8
HBF	ml/min	818±227	623±124	665±161	663±91
RBF	ml/min	591±130	687±151	650±105	875±163

(* = $p < 0.05$ Φ = $p < 0.01$ † = $p < 0.001$)

These data indicate that at safe maintenance doses Db significantly increased CI and peripheral blood flow (UEF) concomitant with a drop in systemic resistance, while Dp increased MAP only. It appears that when inotropic support is desired in the treatment of end-stage congestive cardiomyopathy, Db is the preferable agent.

CLINICAL USEFULNESS AND SAFETY OF THE ERGONOVINE TEST IN PATIENTS WITH CHEST PAIN

R. Charles Curry, Jr., M.D.,F.A.C.C., Carl J. Pepine, M.D. F.A.C.C., James H. Varnell, M.D., Michael B. Sabom, M.D., C. Richard Conti, M.D.,F.A.C.C., University of Florida, Gainesville, Florida

Ergonovine maleate(EM), a vasoconstrictor, has been shown to provoke attacks of Prinzmetal's variant angina(VA) defined as cyclic chest pain with transient ST segment↑ due to coronary artery spasm(CAS). A safe method to detect patients(pts) with VA would be clinically useful in the diagnosis and evaluation of treatment of this disorder. We, therefore, gave EM to 130 pts being evaluated for chest pain during cardiac catheterization and angiography in order to determine the usefulness and safety of the EM test.The pts were divided according to the presence(Group I) or absence (Group II) of VA on clinical presentation. EM(.05-.4mg IV) was given as clinical, ECG, blood pressure, and coronary diameters were studied.

Group	# pts	EM (mg)	chest pain/ ST↑/CAS	Complications
I	10	.05-.2	10	CHB (2), VT (2)
II	120	.2-.4	2	↑↑BP (2)

↑↑BP=>50 mmHg rise in systolic blood pressure,CHB=complete heart block, VT=short burst of ventricular tachycardia

Pts with chest pain and ST↑(>1mm) following EM demonstrated CAS in one or both major coronary arteries with total or subtotal obliteration of the major arterial branch predicted by the ECG. Two pts without VA who responded to EM had severe coronary artery disease(CAD) and a history of rest angina. No serious complications requiring therapy other than sublingual nitroglycerin occurred. Attacks of VA following EM were all relieved in 5-10 min from onset.

Conclusion: EM appears clinically useful and safe in testing for CAS during catheterization and angiography.

TUESDAY, MARCH 7, 1978
AM
CLINICAL APPLICATION OF CROSS-SECTIONAL ECHOCARDIOGRAPHY
8:30 to 12:00

EVALUATION OF MODELS FOR QUANTIFYING LEFT VENTRICULAR SIZE BY 2-DIMENSIONAL ECHOCARDIOGRAPHY

H.L. Wyatt, PhD, Ming Heng, MD, Samuel Meerbaum, PhD, FACC, Robert Davidson, MD, FACC, Eliot Corday, MD, FACC, John Hestenes, PhD, Cedars-Sinai Medical Center, Los Angeles, Calif.

A study was performed to evaluate several mathematical models for quantifying left ventricular (LV) volume and mass using an 84° phased array sector scanner (PASS). In 10 formalin-fixed dog hearts, 6 to 10 short axis and 1 to 2 long axis endocardial outlines from PASS were used to calculate LV volume by Simpson's rule and by formulae derived from an ellipsoidal model. Calculated LV volumes were compared to direct fluid volume determination, ranging from 13 to 109 ml. Results are tabulated (MD= mean difference, SEE=standard error of estimate, r= correlation coefficient, A= LV cross-sectional area. L=LV length from long view, D=LV diameter).

LV MATHEMATICAL MODEL	MD(ml)	SEE(ml)	r
Simpson's rule, all sections	2.7	3.1	.99
A^2/L, one long view	12.5	12.2	.83
D^3, One short view	17.4	25.1	.87
2/3 AL, one short view	7.4	4.2	.98
5/6 AL, one short view	4.2	5.2	.98
$A^{3/2}$, one short view	4.9	7.0	.97

In 12 anesthetized closed-chest dogs, LV mass determined from endocardial and epicardial PASS outlines at end diastole were compared to post-mortem weights, ranging from 78 to 211 gm. Best correlations were obtained with LVV= 5/6 AL (MD=9.0 gm, SEE=9.6 gm, r=.96) and Simpson's rule (MD=9.1 gm, SEE=9.9 gm, r=.95). Conclusion: LV size can be accurately determined with PASS not only by Simpson's rule but also by a simple formula (5/6 AL) using only one short axis section. Satisfactory validation of the latter model facilitates reliable LV quantitation throughout the cardiac cycle

CORRELATION OF REAL TIME 2-DIMENSIONAL ECHOCARDIOGRAPHY WITH POSTMORTEM STUDIES. James L. Weiss, M.D., F.A.C.C., Bernadine H. Bulkley, M.D., F.A.C.C., Grover M. Hutchins, M.D., Steven J. Mason, M.D. The Johns Hopkins Medical Institutions, Baltimore, Maryland.

To assess the accuracy of wide angle phased array 2-dimensional (D) echocardiographic determination of myocardial lesions, comparisons were made between independent 2-D echo readings of left ventricular (LV) function and morphologic evidence of myocardial injury in 14 autopsied patients: 3 had normal hearts; 4, valve disease; and 7, coronary artery disease. Of the 14 patients, 4 had normal myocardium and by echo, normal wall motion or diffuse hypokinesis; ten patients had old or recent myocardial infarction: 4 had small lesions (2 transmural, 2 subendocardial) involving<5% of LV myocardium; 6 large transmural lesions involving>20% of LV myocardium. Of the 10 infarcts, 9 were detected by regional wall motion abnormalities of either akinesis or dyskinesis, and absence of systolic thickening of LV wall. Most myocardial segments immediately adjacent to scar showed wall motion abnormalities suggesting injury, but were morphologically normal. Two small infarcts detected by 2-D echo had been clinically silent. The one infarct which was not detected clinically or by 2-D echo was a healed circumferential subendocardial infarct in a patient with remote valve surgery.

The results suggest that 2-D echo evidence of regional wall motion abnormality and absence of systolic wall thickening is sensitive in detecting segmental myocardial lesions but may overestimate their extent, possibly because segments adjacent to the lesions were reversibly ischemic. This method may not recognize subendocardial injury if it involves the entire left ventricular circumference.

COMPARISON OF M-MODE ECHOCARDIOGRAPHY, CROSS-SECTIONAL ECHOCARDIOGRAPHY AND LEFT VENTRICULOGRAPHY IN PATIENTS WITH CORONARY ARTERY DISEASE

Arthur E. Weyman MD, FACC, Betty C. Corya MD, Mary Jo Black BA, L. Sam Wann MD, Jane E. Marshall BS, Susan Rasmussen RN, Harvey Feigenbaum MD, FACC. Krannert Inst. of Cardiology, Indiana Univ. School of Medicine, and the Veterans Administration, Indianapolis, Indiana

The purpose of this study was to compare the sensitivity and specificity of cross-sectional echocardiography (CSE), M-Mode echocardiography (M-Mode) and right anterior oblique left ventriculography (RAO-LV) in detecting regional wall motion abnormalities in the presence or absence of significant (≥75% narrowing) coronary artery disease (CAD). CSE, M-Mode and RAO-LV studies were independently evaluated for 50 consecutive patients (pts) having technically complete exams. CSE was divided into 5 areas: anterior, posterior, medial, lateral and apical. M-Mode was divided into 3 areas: anterior, posterior and apical. Thirty-five pts had CAD, 13 were normal, and 2 had myocardial abnormalities without CAD. M-Mode, CSE and RAO-LV were all normal for the 13 normal pts. Of 35 CAD pts, M-Mode was abnormal in 20, CSE was abnormal in 19, M-Mode and/or CSE was abnormal in 25 and the RAO-LV was abnormal in 22. Of the 22 pts with abnormal RAO-LV, CSE was also abnormal in 19 while M-Mode was abnormal in 15. M-Mode detected abnormal segments in 5 of 13 CAD pts with a normal RAO-LV. Abnormalities of motion by either technique correlated with location of CAD.

Data shows that the RAO-LV, M-Mode and CSE may not show the same regional abnormalities of the left ventricle in every case. Echocardiography, especially when M-Mode and CSE are combined, detects regional abnormalities at least as often as does ventriculography.

COMBINED PERIPHERAL VENOUS INJECTION AND CROSS-SECTIONAL ECHOCARDIOGRAPHY IN THE EVALUATION OF CARDIAC DISEASE

Anthony N. DeMaria, MD, FACC; William Bommer, MD; Lily George, MD; Alexander Neumann, BS; Lynn Weinert, BS; Dean T. Mason, MD, FACC, University of California, Davis, California

Although the diagnostic value of microcavitations produced by peripheral venous injections of fluid (CONTRAST) during M-mode echography is established, no data are available regarding the usefullness of CONTRAST during cross sectional (2-D) echography. Thus CONTRAST studies were performed during 2-D in 40 catheterized patients (pts): 13 normals (N), 9 pts with right ventricular volume overload due to left to right shunts (L→R), 10 pts with tricuspid regurgitation (TR), 5 pts with severe congestive failure (CHF), and 3 pts with R→L shunt due to Eisenmenger syndrome. CONTRAST during 2-D was analyzed qualitatively in regard to velocity and direction of bubble flow pattern, and quantitatively by spot photometer in reference to the clearance time of bubbles. Following the rapid intravenous injection of 10cc dextrose and water into the brachial vein, a dense shower of microbubbles filled the right atrium and ventricle which were visualized in sagittal section by positioning the 2-D transducer at the cardiac apex. Mean clearance time was similar in N, L→R and EIS: 6, 8, and 8 seconds respectively; but was markedly prolonged in pts with CHF and TR: 19 and 25 seconds ($p<.001$). R→L shunts were clearly visualized from right ventricle (2 pts) and right atrium (1 pt) in EIS. Retrograde velocity and direction of bubble flow from right ventricle to atrium or right atrium to inferior vena cava were observed in 7 of 8 TR pts. Thus, these data demonstrate that 2-D CONTRAST is of great diagnostic value in the identification of patients with intracardiac shunts and tricuspid regurgitation.

INDICATOR-DILUTION CURVES OBTAINED BY PHOTOMETRIC ANALYSIS OF TWO-DIMENSION ECHO-CONTRAST STUDIES

William Bommer, MD; James Neef; Alexander Neumann, BS; Lynn Weinert, BS; Garrett Lee, MD; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, Univ. of Calif., Davis, CA

The ability of cross-sectional echocardiography (2-D) to visualize microcavitations induced by the venous injection of fluid provides the opportunity to quantitatively assess intracardiac blood flow. Accordingly, we undertook to develop a system to quantify the appearance and decay characteristics of a bolus of intracardiac microcavitations. An analog photometer was focused upon the screen of the 2-D monitor and sampled the mid right ventricle (RV) which was visualized in the hemiaxial projection. The rapid injection of 10 cc dextrose in water produced a flood of microbubbles which filled the RV cavity on 2-D. The time course of appearance and decay of the echo reflections from the microcavitations was measured by the photometer whose analog signal was recorded photographically to yield records similar to indicator dilution dye curves. The resultant curves were analyzed for time from peak concentration to 50% (DT50) and 90% decay (DT90). Multiple curves were obtained in 35 patients (pts) and were reproducible with an accuracy of 15%. DT90 correlated with cardiac output by indicator dilution ($r = 0.80$) and DT90 of pts with low (<2.5 l/min/m^2) cardiac index was significantly less than in patients with normal indices, 14.1 vs 5.6 seconds ($p<.01$). DT90 distinguished patients with from those without catheter documented tricuspid regurgitation (TR), 26.0 vs 3.5 seconds ($p<.001$) and no TR patient had a DT90 of <10 seconds. Thus, a method has been devised to obtain indicator dilution type curves from photometric sampling of the signal induced by microcavitations on 2-D echogram. Analysis of the appearance and decay characteristics of such curves may provide non-invasive information regarding cardiac output.

DETECTION OF RHEUMATIC MITRAL REGURGITATION USING CROSS-SECTIONAL ECHOCARDIOGRAPHY

L.S. Wann, M.D., Harvey Feigenbaum, M.D., FACC, Arthur E. Weyman, M.D., FACC, James C. Dillon, M.D., FACC, Indiana University School of Medicine, Indianapolis, Indiana

Short-axis, cross-sectional echocardiograms of the mitral valve were performed in twenty consecutive patients with rheumatic mitral valve disease in order to determine if mitral regurgitation could be detected. Four cross-sectional echocardiograms were technically inadequate. Eight of the remaining patients had no significant mitral regurgitation by cineangiography; eight had significant mitral regurgitation. Two independent observers reviewed video tapes of the cross-sectional echocardiograms without knowledge of the cineangiograms or clinical findings. In each case, the presence of significant mitral regurgitation was correctly predicted by viewing the cross-sectional echocardiograms. The thickened leaflets of the mitral orifice could be easily identified in both diastole and systole. Closure of the two leaflets was best observed early in systole before caudad movement of the annulus caused the orifice to move out of the ultrasonic beam. Complete closure of the leaflets was seen in patients without mitral regurgitation. Failure of small areas of either the medial or lateral aspect of the valve to close was associated with insignificant mitral regurgitation. Failure of both sides to close or failure to close in the center of the valve indicated significant mitral regurgitation. We conclude that significant mitral regurgitation in patients with rheumatic mitral valve disease can be detected by qualitative analysis of short axis cross-sectional echocardiograms.

ASSESSMENT OF SEPTAL MYECTOMY IN HYPERTROPHIC SUBAORTIC STENOSIS BY SINGLE- AND TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Jay N. Schapira, MD; Randolph P. Martin, MD; Dale R. Stemple, MD; Harry Rakowski, MD; Edward B. Stinson, MD, FACC; Richard L. Popp, MD, FACC, Cardiology Division and Cardiovascular Surg. Dept, Stanford Med. Ctr. Stanford CA.

Although the hemodynamic effects of septal myectomy (SM) in hypertrophic subaortic stenosis (HSS) have been documented, the expected thinning of the interventricular septum (IVS) post-SM has seldom been observed previously by M-mode echocardiography (MME). To analyze this we reviewed 16 HSS patients (pts) who underwent extensive SM at Stanford from 1973-77. Marked post-SM reduction or abolition of outflow gradients in 16/16 pts was associated with decreased end-diastolic IVS thickness at the mid-ventricular level in 14/16 pts and at the subaortic level in 16/16 pts by MME. The group also showed changes in mitral valve systolic anterior motion, mitral E-F_O slope, left ventricular outflow dimensions, and percent diameter shortening with both MME and two-dimensional studies. In all 6 pts having two-dimensional echocardiography, SM did not involve the papillary muscles. In the left ventricular short axis view the SM was confined to 10-12 o'clock on the left ventricular circumference, and the shape and extent of SM was defined. Limited SM confined to the subaortic area was recognized by two-dimensional echocardiography in the 2 pts with lack of IVS thinning by MME at the usual mid-ventricular level. Our analysis suggests the apparent lack of IVS thinning by MME in prior work may have been due to (1) inaccessible position of SM; (2) failure to investigate the accessible medial subaortic portion of the IVS with the MME beam; and/or (3) SM more narrow than the ultrasound team. Two-dimensional echocardiographic studies are useful for pre-operative planning and post-operative assessment of the extent and location of SM in HSS pts.

ULTRASONIC CLASSIFICATION OF CARDIOMYOPATHIES

Robert E. Fowles, MD; Randolph P. Martin, MD; Jay N. Schapira, MD; Richard L. Popp, MD, FACC, Div. of Cardiol., Stanford Medical Center, Stanford CA.

We have utilized two-dimensional echocardiography (2D) to derive a system for classifying underlying anatomy which helps clarify the often cloudy clinical picture of cardiomyopathy (CM). Medical records and 2D studies were reviewed on 56 patients (pts) presenting over 18 months with referring diagnoses which included CM. Symptoms, physical exam, X-ray, ECG, and eventual diagnosis were correlated with a 2D-derived classification scheme. Classification was according to presence of cardiac dilation (Dil), presence and symmetry of wall hypertrophy (Hyper), and presence of any left ventricular segmental contraction abnormalities (Seg).

This classification system highlights lack of specificity of symptoms and signs in CM relative to anatomy defined by 2D and final diagnosis, e.g.:

	No.	Dyspnea	Gallop	X-ray Cardiomegaly
Dil,Non-Hyper,Seg	15	93%	87%	87%
Dil,Non-Hyper,Non-Seg	10	100%	80%	70%
Non-Dil,Hyper,Seg	17	71%	47%	53%

Amyloid CM showed symmetrical and ultrasonically distinct hypertrophy. 2D recognition of contraction patterns did not always distinguish between pts with "idiopathic congestive" CM and ischemic CM.

2D is well suited for determination of contraction patterns, wall structure, wall thickness, ventricular shape, and visualization of all cardiac chambers. Classification of anatomy by noninvasive means has clarified pathophysiology and narrowed the differential diagnosis of CM in our pts. We believe this supplements the clinical features previously used to segregate forms of CM.

ECHOCARDIOGRAPHIC CLASSIFICATION OF HYPERTROPHIC CARDIOMYOPATHY

Brian W. Gilbert, MD, FACC; Allan G. Adelman, MD; Andrew J. Buda, MD; Garry W. MacKenzie, MD; Denton M. Corrigal, MD; E. Douglas Wigle, MD, Toronto General Hospital, Toronto, Ontario

Sixty-seven patients with hypertrophic cardiomyopathy, classified hemodynamically into non-obstructive(NON)(15), latent obstructive(LAT)(20) and resting obstructive(REST)(32), were studied by conventional echocardiography. Systolic anterior motion(SAM) of the anterior mitral leaflet was quantitated and found to be severe in most REST's (27/32), mild or moderate in all LAT's and minimal or absent in NON's. The septum was thickest in the REST's (24.5 $\pm$ 3.1), thinner in the LAT's (20.2 $\pm$ 2.1) and thinnest in the NON's (17.5 $\pm$ 2.2) while the posterior wall was increased (13.3 $\pm$ 1.3) only in REST. Aortic valve cusp notching (23/31) was only found in REST. The septum-anterior mitral leaflet dimension at onset of systole was narrowest in the REST's (14.3 $\pm$ 3.8), wider in the LAT's (19.7 $\pm$ 3.4) and widest in the NON's (22.5 $\pm$ 3.9). The anterior mitral leaflet-posterior wall distance at onset of systole was significantly increased in patients with REST (22.1 $\pm$ 4.4) as compared to normals (15.6 $\pm$ 3.2) suggesting anterior displacement of the mitral apparatus.

As explained by the Venturi mechanism, outflow tract obstruction is more likely to be present with a thicker septum and with a narrower septum-anterior mitral leaflet dimension. When these and other parameters are examined, it is possible to echocardiographically classify most patients with hypertrophic cardiomyopathy.

DETECTION OF TRICUSPID REGURGITATION WITH CONTRAST TWO-DIMENSIONAL ECHOCARDIOGRAPHY

William M. Lieppe, MD; Victor S. Behar, MD, FACC; Ralph Scallion, MD; and Joseph Kisslo, MD; Duke University Medical Center, Durham, North Carolina

The diagnosis of tricuspid regurgitation (TR), on the basis of clinical findings, is often difficult to make with certainty. In the present study, contrast echocardiography (CE), utilizing a phased array two-dimensional ultrasound system and peripheral venous injections of 10 ml saline was evaluated for the detection of TR. The appearance of microcavitations in the inferior vena cava and the back and forth movement of microcavitations across the tricuspid valve were considered evidence for TR. Microcavitations were clearly visualized in all patients (PTS) included in this series. Thirty PTS were included and were assigned, on the basis of physical examination and jugular pulse tracing, to one of three groups: Group I included five PTS whose clinical findings were diagnostic for TR, Group II included 15 PTS whose clinical findings were equivocal for TR but in whom the recognized primary problem was frequently associated with TR, Group III was composed of 10 PTS without clinical suggestion of TR. All Group I PTS had positive CE studies for TR, while all Group III PTS had negative studies, suggesting that this technique may be specific for TR. In Group II, eight PTS manifested TR by CE, while seven PTS did not. Of particular note were three Group II PTS who had positive CE studies despite the absence of specific clinical findings for TR, suggesting that this technique may be more sensitive than the methods in common use.

ABNORMALITIES OF INTERVENTRICULAR SEPTAL MOTION FOLLOWING CARDIAC SURGERY. CROSS-SECTIONAL ECHOCARDIOGRAPHIC STUDIES. Richard Kerber, MD, FACC; Donald Doty, MD, CV Cent and CV Div, Depts of Med and Surg, Univ of Iowa Hosp, Iowa City, Ia.

The interventricular septum frequently shows abnormal motion by echocardiography after cardiac surgery. Possible mechanisms include changes in ventricular shape, changes in total intrathoracic cardiac motion or sternal-cardiac adhesions. Fourteen patients undergoing mitral or aortic surgery (12) or VSD repair (2) were studied preop and early (5-14 days) postop by M-mode echo and by a real-time 30° sector-scanner. None had coronary disease. All had normal interventricular septal motion (IVSM) preop; 8 developed abnormal IVSM postop. No consistent ventricular shape changes were seen whether the postop septal motion was normal or abnormal. Short-axis cross-sectional echoes were measured to obtain chamber size and the maximum end-diastolic and end-systolic posterior epicardial distance from the transducer. The difference between the two distances indicated systolic epicardial excursion. Systolic epicardial excursion was greater postop in abnormal septal motion patients (abnormal: 0.5±.1 vs normal: 0.0±.1 cm*) (*=p<.05), suggesting they have an anterior motion of the entire heart which overbalances the normal posterior systolic IVSM and results in a net abnormal IVSM. Right ventricular diameters were larger in abnormal patients both preop (abnormal: 4.0±.6 vs normal: 2.4±.4 cm*) and postop (abnormal: 4.4±.6 vs normal: 2.9±.3 cm*). The larger right ventricles may promote the development of right ventricular-sternal adhesions. Conclusions: postop abnormal IVSM results from abnormal total intrathoracic cardiac motion, contributed to by right ventricular-sternal adhesions.

EVALUATION OF BICUSPID AORTIC VALVES BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY
Navin C. Nanda, MD, FACC; Raymond Gramiak, MD, University of Rochester Medical Center, Rochester, NY

Eleven patients with proven bicuspid aortic valves (BAV) were studied by a new wide angle (60°) mechanical sector scanner. Both long axis and transverse scans of the aortic root were obtained. On transverse scans the most prominent findings were the presence of an eccentric diastolic cusp position and diastolic folding of the cusp margins which showed alterations in shape from beat to beat. None showed the presence of a third commissure, although in some instances a prominent raphe could be seen. Patients with stenosed valves also showed, on long axis scans, valve doming in systole with a central or eccentric orifice and supravalvar aortic dilatation. Transverse scans of the aortic root at the level of the body of the dome revealed a circular configuration of the dome cross-section situated within the aortic root producing a "circle within a circle" (c-c) appearance. During diastole, this pattern changed as the dome began to collapse, resulting in irregular, wavy linear echoes produced by the folds of the cusp margins. Fifteen patients with tricuspid aortic valves (TAV) examined in a similar manner served as control. Three cusps could be identified in 10 and none showed folding of cusp margins. Three patients with TAV and aneurysmal dilatation of aortic root/sinus of Valsalva showed cusp diastolic eccentricity and a c-c appearance resulting from the inability of the cusps to coapt with the walls of the enlarged aorta, but were distinguished from BAV by the absence of folds on the cusp margins. Two-dimensional echocardiography provides an explanation for the findings observed on M-mode echo studies and adds greater specificity to the diagnosis of a BAV.

TUESDAY, MARCH 7, 1978
AM
ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY—I
8:30 to 12:00

EFFECT OF DRUGS IN WPW SYNDROME. IMPORTANCE OF INITIAL LENGTH OF EFFECTIVE REFRACTORY PERIOD OF ACCESSORY PATHWAY.
Hein J. Wellens M.D., F.A.C.C., Frits W. Bär M.D., Anton P. Gorgels M.D., Department of Cardiology, Annadal Hospital and University of Limburg, Maastricht, The Netherlands.

Effect of drugs on the Effective Refractory Period of the Accessory Pathway (ERP_{AP}) in A-V and V-A direction was studied in relation to length of ERP_{AP} prior to drug administration. Procainamide(Pr) 10 mg/kg bodyweight (bw), Quinidine (Q) 4 mg/kg bw, Ajmaline (Aj) 50 mg i.v. and Amiodarone (Am) 100 mg orally 3x daily during 2 weeks was given to respectively 16, 10, 18 and 15 patients (p). All p were studied by intracavitary recordings and programmed electrical stimulation of the heart using identical basic cycle lengths before and after drug administration. P were divided into those with ERP_{AP} < 270 msec (Group I) and ≥ 270 msec (Group II).
Results: 1) In Group I Pr, Q, Aj and Am lengthened ERP_{AP} in A-V direction in 5, 3, 6 and 11 out of 9, 5, 9 and 11 p, and in V-A direction in 6, 4, 4 and 6 out of 10, 8, 10 and 10 p. In Group II this was observed in A-V direction in 7, 5, 9 and 4 out of 7, 5, 9 and 4 p, and in V-A direction in 5, 1, 7 and 3 out of 5, 1, 8 and 5 p.
2) Mean increase in ERP_{AP} in A-V and V-A direction was much less in Group I (resp. 43±31 and 56±41 msec) as compared to Group II (244±71 and 111±101 msec).
3) Am was most effective in lengthening ERP_{AP}.
Conclusions: 1) Magnitude of increase in length of ERP_{AP} after drug administration is related to initial length of ERP_{AP}. 2) Only modest lengthening of ERP_{AP} can be accomplished by drug administration in p with short ERP_{AP}. 3) In reporting on effect of drugs in p with WPW importance of initial length of ERP_{AP} should be realized.

USE OF AJMALINE IN IDENTIFYING PATIENTS WITH SHORT REFRACTORY PERIOD OF THEIR ACCESSORY PATHWAY IN WOLFF-PARKINSON-WHITE SYNDROME.
Frits W. Bär M.D., Herman L. Frank M.D., Anton P. Gorgels M.D., Eef H. van der Heijden M.D., Jacques J. Schmitz M.D., Hein J. Wellens M.D.,F.A.C.C., Department of Cardiology, Annadal Hospital and University of Limburg, Maastricht, The Netherlands.

Ajmaline has a short lasting (less than 1 hour) lengthening effect on the Effective Refractory Period (ERP) of the Accessory Pathway (AP) in patients (p) with the Wolff-Parkinson-White (WPW) syndrome. Fifty mg of Ajmaline was injected intravenously over a 3 min. period in 59 consecutive p with the WPW syndrome, 24 hours prior to a programmed electrical stimulation study (PES). During PES ERP_{AP} was determined.
Results: Following Ajmaline injection 32 p (group I) developed complete block in their AP. In this group ERP_{AP} ranged from 230 to 520 msec (7 p with an ERP_{AP} ≤ 270 msec), mean 327 ± 70 msec. In the 27 p (group II) in whom conduction over the AP persisted following Ajmaline injection ERP_{AP} ranged from 170 to 290 msec (1 p with ERP_{AP} > 270 msec), mean 233 ± 28 msec. The difference in mean ERP_{AP} between group I and II was highly significant ($p < 0,0001$).
Conclusions: Our data indicate that failure to achieve complete block in the AP by 50 mg Ajmaline intravenously is highly suggestive for a short ERP_{AP} in patients with the WPW syndrome. This test, which can easily be performed in the office is therefore useful to identify patients with WPW who are at risk of sudden death if atrial fibrillation supervenes.

NATURAL AND EVOKED ATRIAL FLUTTER DUE TO CIRCUS MOVEMENT IN DOGS

John P. Boineau, MD, FACC; Charles R. Mooney, MA; Anita C. Wylds, BS; Roger D. Hudson, BEE; Carey B. Miller, MSEE, Medical College of Georgia, Augusta, Ga.

Natural atrial flutter (AFL) was discovered in a dog. The observations in this dog led to studies in a series of dogs in which the extrastimulus technique was used to evoke runs of repetitive activity resembling AFL. Epicardial atrial activation maps were made from 72-96 bipolar complexes recorded during the arrhythmias. Multiple effective refractory periods were determined and these values were used to construct maps of the refractory period distribution. Dog #1 with true AFL demonstrated a complex form of circus motion characterized by unidirectional block and one-way conduction. Abnormal slowing of the unblocked, circus wave stabilized and maintained the repetition by permitting more time for recovery of a uniform state of excitability ahead of the wave. The slow conduction in dog #1 was associated with discontinuity in the preferential atrial conduction pathways. The circus activation patterns in the dogs with evoked AFL were similar to those in true AFL; however, cycle lengths were shorter and the circus wave conducted faster. In evoked AFL, the regional differences in refractory period duration determined the one-way block and circus conduction patterns. The circus pattern was caused by a nonuniform, bimodal refractory state of the atrium which simultaneously exerted a blocking effect while permitting conduction and complex shaping of the unblocked wave, which was routed back to its site of origin. Thus, AFL was the result of 3 interacting factors: 1) atrial premature beat, 2) nonuniform distribution of atrial refractory periods, 3) slow conduction of the circus wave initiated by factors 1 and 2.

ST SEGMENT CHANGES ACROSS AN ISCHEMIC BORDER, AS DEFINED BY NADH FLUORESCENCE PHOTOGRAPHY

Michael B. Simson, MD; Wesley R. Harden, III, MD; Clyde Barlow, PhD; Alden H. Harken, MD, FACC, University of Pennsylvania, Philadelphia, Pa.

Epicardial ischemia was identified by reduced nicotinamide adenine dinucleotide (NADH) fluorescence photography. This technique visually marks areas of intra-mitochronrial anoxia and was used to study ST segment changes across an ischemic border. In eight isolated rabbit hearts (Langendorf preparation) a left ventricular (LV) ischemic area was produced by coronary artery ligation. A roving platinum electrode and the ischemic area were simultaneously recorded (295 trials) by NADH fluorescence photography. After perfusion with fluorescein and rapid freezing, serial sections revealed that the ischemic area was transmural, uniform and confined to the LV free wall.

As the ischemic border was approached, ST segment elevation increased progressively (space constant 3.5 mm). ST segment elevation peaked 3 mm within the ischemic border, then declined. No polarity reversal was seen at the ischemic border. ST segment negativity was not detected immediately outside the ischemic border.

We conclude: 1) the ischemic border is narrow (<0.1 mm) as identified by NADH fluorescence. 2) ST segment changes across an ischemic border are not explained by solid angle analysis. 3) ST segment changes give relatively imprecise location of an ischemic border. 4) ST segment changes are gradual at the ischemic border and suggest a spuriously wide border zone.

MECHANISMS OF TACHYARRHYTHMIAS IN THE LOWN-GANONG-LEVINE SYNDROME

Agustin Castellanos, MD, FACC; Ruey J. Sung, MD, FACC; Januarisz Styperek, MD; Robert J. Myerburg, MD, FACC, University of Miami School of Medicine, Miami, Florida.

Paroxysmal supraventricular tachycardia (PSVT) and atrial flutter-fibrillation (AF) occur frequently in patients (pts) with the Lown-Ganong-Levine (LGL) syndrome.However, the underlying mechanisms responsible for these arrhythmias are not well understood. We systematically analyzed electrophysiological findings in 18 consecutive LGL pts with episodes of palpitations associated with a short P-R interval ($\leq$ 0.12 sec) and a normal QRS complex. During sinus rhythm, all had abbreviated atrioventricular (AV) nodal conduction time (A-H interval$\leq$ 50 msec).PSVT could be elicited during programmed atrial premature stimulation in 8 pts. Of these, 5 pts had AV nodal reentrant tachycardia using a slow pathway for antegrade and a fast pathway for retrograde conduction, and 3 pts had circus movement tachycardia involving the normal AV pathway and a left sided accessory AV bypass tract (Kent bundle) capable only of retrograde conduction.Atrial vulnerability, as demonstrated by the development of repetitive atrial responses or AF at short atrial premature coupling intervals (A1-A2$\leq$320 msec) was present in 7/18 pts. Rate acceleration (250/min) during PSVT, and rapid ventricular response (250-300/min) during AF, were observed in 2 and 4 pts, respectively.Although the etiology of abbreviated AV nodal conduction time remains unsettled, it can be concluded from results of this study that: (1) the occurrence of AF is related to atrial vulnerability and (2) the genesis of PSVT can be accounted for by the presence of dual AV nodal pathways or a concealed accessory AV bypass tract in the LGL syndrome.

ELECTROCARDIOGRAPHIC DETECTION OF INTRINSIC LOCAL VENTRICULAR RECOVERY PROPERTIES

Paul M. Urie, PhD; Mary Jo Burgess, MD; Robert L. Lux, PhD; J.A. Abildskov, MD, FACC; University of Utah, Salt Lake City, Utah

The body surface distributions of QRS, ST-T and QRST areas from 192 simultaneously recorded ECGs were determined in 11 dogs during 2 to 25 activation sequences produced by ectopic ventricular stimulation. Pooled variance of the QRS and ST-T areas were each 10 times greater than that of QRST areas ($P<0.005$) demonstrating the QRST area to be largely independent of activation sequence and dependent on intrinsic recovery properties. The body surface patterns of QRST area were compatible with electrotonic effects of activation on recovery further suggesting QRST area to be an index of recovery properties. Findings were applied to a study of the human heart by determining distributions of deflection areas in 70 normal subjects during sinus rhythm. Pooled variances were QRS 72.7, ST-T 156.2 and QRST 245.0 mv msec. Since experimental results indicated QRST areas reflected recovery properties, findings in humans suggest that normal variability of these properties exceeds that of activation sequence. They further show this information is not evident from the ST-T deflection alone since variance of that quantity was less than that of the QRST. The distribution of QRST areas provides a new criterion for definition of the normal ECG in terms of ventricular recovery properties and a means of recognizing abnormal properties. Since findings were based on ECG sampling with demonstrated regional cardiac sensitivity, they suggest that local inequalities of recovery related to myocardial infarct size and arrhythmia vulnerability may be recognizable from body surface distributions of QRST area.

EXPERIMENTAL REPRODUCTION OF THE LONG Q-T SYNDROME

Peter J. Schwartz, MD, FACC, Cardiovascular Research Institute, University of Milan, Italy.

We have previously suggested that the long Q-T syndrome (LQTS) may depend upon a congenitally lower than normal right cardiac sympathetic activity with a reflexly increased left-sided activity. Right stellectomy (RSGx) increases ventricular excitability and vulnerability to fibrillation in anesthetized animals. Since emotion is a crucial stimulus in provoking syncopal attacks in LQTS patients, we have studied cats during naturally elicited emotional behavior before and after RSGx. Preliminary results in 15 cats chronically instrumented for ECG and blood pressure recordings indicate that emotion in intact cats produces only sinus tachycardia. After RSGx the QT interval lenghtens and the most common response to emotion is A-V nodal tachycardia. In some cats it has also been possible to elicit frequent premature ventricular beats and even ventricular tachycardia. These abnormal responses were still reproducible two months after RSGx and were completely suppressed by either beta-blockade or left stellectomy. The induction of life-threatening arrhythmias during emotion in conscious cats whose only abnormality is a deficit of right cardiac sympathetic innervation may be considered an experimental reproduction of LQTS. These results strenghten our pathogenetic hypothesis and increase the rationale for beta-blockade and/or left stellectomy as therapy of choice for LQTS. It is noteworthy that left stellectomy suppressed syncopal attacks refractory to medical therapy in 11 out of 11 patients with LQTS.-

SINOATRIAL CONDUCTION: THE EFFECTS PRODUCED BY A CHANGE IN SITE OF STIMULATION

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Sinoatrial conduction time (SACT) can be directly measured or estimated using the extrastimulus technique. However, limited data is available on the effects of stimulation site on SACT. Therefore, studies were performed in 18 rabbit sinus node preparations using standard microelectrode technique and premature stimulation at 3 sites: crista terminalis (CT), coronary sinus (CS) and atrial septum (AS). Two populations were seen with CS stimulation: with (A) and without (B) pacemaker shift. In (A), the curves of normalized sinus and atrial return cycles were shifted upwards compared to CT stimulation, and the sinus node was captured by APD's later than at the transition point. The SACT for the (B) group was significantly shorter than CT SACT, (CT, 52.5±5.0 msec; CS (B),43.6±3.7 msec, $p < 0.05$). In group (B), estimated CT and the transition point were different from CT data. AS stimulation shortened retrograde conduction (CT, 19.7±1.1 msec; AS, 15.7±1.0 msec, $p < 0.005$), and lenghened antegrade conduction (CT, 32.5±2.5 msec; AS, 34.7±2.8 msec, $p < 0.005$). Estimated conduction time was shortened (CT, 57.8±6.3 msec; AS, 43.6±4.8 msec, $p < 0.01$), and the transition point shifted to the right. Paradoxical shortening of SACT with CS stimulation may be related to a special retrograde conduction wavefront and pacemaker shift. AS stimulation data may be explained by proximity to specialized atrial pathways. The changes in SACT related to stimulation site have important clinical implications.

QT INTERVAL IN IDIOPATHIC PROLAPSED MITRAL VALVE

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The mechanism underlying the high incidence of arrhythmias in patients with idiopathic prolapsed mitral valve (PMV) is not definitely determined. The association of S-T & T wave abnormalities with or without QT prolongation in some patients have been reported. Since delayed repolarization may be responsible for arrhythmias in PMV it was decided to examine the QT interval in 54 patients in whom midsystolic clicks were recorded by phonocardiography, in addition to angiography in 43; only patients with idiopathic PMV were included. 13 patients had mitral insufficiency. Atrial arrhythmias were present in 7, frequent PVC in 6, paroxysmal ventricular tachycardia and fibrillation in one patient. None were receiving quinidine, 3 were taking digoxin, and all had normal electrolytes. The longest QT interval in 12 lead EKG was measured in at least 2 recordings taken at different dates. The QTC was calculated from Brazett formula and compared with the normal values adapted from Lepeschkin & Ashman. Our results show that QT and QTC intervals for the whole group matched for age, sex & heart rate were significantly longer than the mean and upper limits of normal for QT ($P<0.001$). The QTC in all patients exceeded the mean normal level (range 6-30 msec mean 13±5) and in 53 patients it exceeded the upper limits of normal (range 3-27 msec mean 10±6). One patient with prolonged QT (+ 150%) developed ventricular fibrillation after quinidine therapy. In conclusion, delayed repolarization expressed as QT prolongation is a common association in idiopathic PMV. To elicit such abnormality repeated measurement of QT interval should be made. In presence of significantly prolonged QT, drugs that cause further delay in repolarization should be avoided in management of associated arrhythmias.

CATHETER RECORDINGS OF SINOATRIAL NODE POTENTIALS IN THE IN SITU CANINE HEART.

Marvin Cramer MD, Robert J. Hariman MD, Robert A. Boxer MD, Ehud Krongrad MD FACC, and Brian F. Hoffman MD. Columbia University, College of Physicians and Surgeons, New York, New York.

We used conventional bipolar platinum recording catheters (interelectrode distance 15 mm) and high gain D.C. amplification (filter settings 0.5-30 Hz) to record extracellular potentials of the canine sinoatrial node (SAN) from the endocardial surface of open chest dogs. The catheter was introduced from the right jugular vein and positioned along the crista terminalis. Two low frequency low amplitude potentials were recorded. The potentials were also recorded from the same site on the epicardial surface and were identical to SAN electrograms we previously described in isolated preparations of rabbit and canine SAN. Transient asystole was produced by infusion of KCl solution (10mEq/L) into the SAN artery. During the infusion the SAN electrogram showed complete dissociation of the low frequency SAN potentials from the high frequency atrial potentials. These changes were similar to those previously seen in isolated SAN preparations during complete sinoatrial block. The experiment demonstrates the feasibility of recording reliable SAN electrograms with catheters and suggests that similar records may be obtainable in man.

A TRANSVENOUS CATHETER ELECTRODE TECHNIQUE FOR NEURAL MODULATION OF SINUS RATE AND A-V CONDUCTION

Terry B. Cooper, MD, Gilbert R. Hageman, PhD, Thomas N. James, MD, FACC, and Albert L. Waldo, MD, FACC, University of Alabama, Birmingham, Ala.

The effects on sinus rate and A-V conduction of high frequency (20 Hz) bipolar pacing (HFP) from the right pulmonary artery (RPA) were studied in 9 dogs. For each study, a His bundle electrogram, atrial electrograms and an ECG were recorded simultaneously during HFP from a multipolar catheter electrode passed transvenously to the RPA. With RPA HFP during sinus rhythm: 1) the control sinus rate (mean 158 ±2 beats/min) slowed significantly (92 ±8 beats/min) ($P < 0.001$); 2) A-V block was not observed. With RPA HFP during atrial pacing at a rate faster than the sinus rate, 1st and 2nd degree A-V block proximal to the His bundle electrogram recording always occurred. With RPA HFP during atrial fibrillation sustained by rapid atrial pacing, the control ventricular rate (mean 167 ±6 beats/min) slowed significantly (65 ±8 beats/min) ($P < 0.001$). The RPA site from which HFP produce the maximal effects on sinus rate and A-V conduction was localized easily and reproducibly by fluoroscopic position of the catheter electrode and the recording of characteristic electrograms from the catheter electrode. The extent of sinus slowing and A-V block could be adjusted by varying the stimulus strength (range 1-50 ma). These effects were blocked by intravenous atropine or hexamethonium and were not blocked by decentralization of the cervical vagi, demonstrating that the RPA HFP effects are via cardiac efferent parasympathetic preganglionic neurons. In conclusion, HFP from an easily identifiable RPA site using a bipolar catheter electrode may be used to influence cardiac rate and rhythm.

TUESDAY, MARCH 7, 1978
AM
EXERCISE STRESS TESTING
8:30 to 12:00

VALUE OF A MULTIVARIATE APPROACH FOR INTERPRETING TREADMILL EXERCISE TESTS IN CORONARY ARTERY DISEASE

Julian L. Berman, MD; Joshua Wynne, MD; Peter F. Cohn, MD, FACC, Peter Bent Brigham Hospital, Boston, MA.

To determine the value of a multivariate approach for interpreting treadmill exercise tests (TET), 204 patients (pts) referred for evaluation of chest pain were studied with a standard Bruce protocol TET and coronary arteriography. Sixty-three pts had normal coronary arteriograms (NCA) and 141 pts had coronary artery disease (CAD). Positive TET = depression (↓) of ST segment ≥ 1 mm (116 pts), negative TET = 0 - 0.9 mm ST↓ with > 85% maximum predicted heart rate (HR)(49 pts), and non-diagnostic TET = neither of the above (39 pts). Predictive value (PV) of a positive TET for CAD was 43/55 (78%) using 1 mm ↓, compared with 59/61 (97%) using ≥ 2 mm ↓. However, when the 1 mm criterion was combined with either blood pressure (BP)-HR product < 23,000, duration of TET < 6 minutes or persistence of ST↓ > 3 minutes, the CAD PV increased to 80-89%, and in pts with any 2 of the above, the PV was 89%. PV in all positive TET for multivessel CAD was highest using duration of TET and/or BP-HR product (86-93%). PV of a negative TET for NCA was 29/49 (59%) and could be increased with duration of TET > 8 minutes and BP-HR product > 28,000 (67-100%). However, only 8/49 (16%) had multivessel CAD. PV of a non-diagnostic TET for NCA was 19/39 (49%). Presence of chest pain during TET did not increase PV of positive, negative, or non-diagnostic TET. This study suggests that the PV for CAD of a < 2 mm positive TET and the PV for NCA of a negative TET can be improved with a multivariate approach.

A METHOD FOR RECORDING OF EXTRACELLULAR SINOATRIAL ELECTROGRAMS DURING CARDIAC SURGERY IN MAN.

Robert J. Hariman MD, Ehud Krongrad MD FACC, Robert A. Boxer MD, Marvin Cramer MD, Frederick O. Bowman Jr. MD, James R. Malm MD and Brian F. Hoffman MD. Depts. of Pharmacology, Pediatrics and Surgery, College of P&S, Columbia University, New York, N.Y. 10032.

The ability to record extracellular electrograms (E) of the sinoatrial node (SAN) in man will provide insight into normal and abnormal function of human SAN. In parallel with the technique for recording of extracellular SAN E on in situ canine hearts developed in our institution, we designed an electrode probe containing 3 pairs of "modified unipolar electrodes". Each pair consisted of a recording electrode (RE) and an indifferent electrode (IE) 6,7 and 8 mm apart from each other. We studied 10 patients (age 18 mos - 52 yrs) with various forms of heart disease (6 with congenital heart disease and 4 with coronary artery disease) during cardiac surgery (CS). To record SAN E, the REs were placed on the sulcus terminalis on the anticipated location of the SAN, while the IEs on the epicardial surface of the free right atrial wall. DC amplifiers with filter settings between 0.5 and 30 Hz, high amplification and a paper speed of 100 mm/sec were used. Human SAN E were obtained in 7 of the 10 patients, and were found to have similar characteristics as the previously reported rabbit and canine extracellular SAN E. Two distinct slopes preceded the P wave of the simultaneously recorded scalar electrocardiogram i.e. a slow diastolic slope and a more rapid upstroke slope. Our newly described technique may be useful for 1)localization of the SAN during CS in patients in whom injury to the SAN is likely, and 2) evaluation of normal and abnormal responses of the SAN to interventions during CS.

THE FALSE POSITIVE TREADMILL TEST: IDENTIFICATION BY CARDIOKYMOGRAPHY

Robert Silverberg MD; Dan Tzivoni MD; Ran Vas, PhD; George Diamond MD; James Forrester MD, FACC. Cedars-Sinai Medical Center, Los Angeles, California

There is a high incidence of false positive electrocardiographic treadmill tests among asymptomatic individuals. Stress induced segmental myocardial wall motion (SWM) abnormalities are specific for ischemia. The usefulness of this parameter in conjunction with diagnostic treadmill testing was evaluated in 54 catheterized normal pts. (33 males, 21 females). All pts. were studied during submaximal treadmill testing by cardiokymography (CKG), a new noninvasive technique that detects SWM by distortion of an induced electromagnetic field. Recordings were obtained over precordial position V_4 at rest and every 2 min. following exercise in conjunction with the 12 lead ECG. The CKG response was characterized as to normal (systolic inward motion) or abnormal (systolic outward motion). 2 pts. were excluded because of an abnormal resting CKG. 16 pts. had false positive (FP) TM-ECG tests by standard criteria (>1 mm. horizontal ST depression) and all but one had a CKG response interpreted as normal. There were 3 FP TM-CKG's and 2 of these had true negative TM-ECG's. ECG specificity was 69%, whereas CKG specificity was 94% ($p < .01$). 34/52 (65%) pts. had concordantly true negative ECG-CKG tests and only 1 normal pt. had a concordantly false positive ECG-CKG test. Exclusion of 10 pts. with inadequate stress tests (<90% predicted maximum heart rate) caused the specificity to fall slightly (91% for the CKG, 62% for the ECG), although the sensitivity rose. (In 70 CAD pts. not part of this study, CKG sensitivity was 74% and ECG sensitivity was 59% ($p<0.01$)). The data suggests that use of cardiokymography, in conjunction with ECG treadmill testing, allows identification of false positive stress tests and improves diagnostic accuracy.

EFFECT OF SUBMAXIMAL EXERCISE ON VULNERABILITY TO FIBRILLATION IN THE CANINE VENTRICLE

Albert K. Dawson, PhD, Medtronic, Inc., Minneapolis, MN, and Arthur S. Leon, MD, FACC, University of Minnesota, Minneapolis, MN.

The risk of instantaneous cardiac death (ID) due to ventricular fibrillation was compared in resting and exercising dogs. Bipolar electrodes were implanted in the left ventricular myocardium and a reversible snare placed around the left anterior descending coronary artery. Three weeks later all dogs were randomly assigned to either an exercise (E) (13 dogs)or a control (C) (12) dogs) group. Ventricular fibrillation thresholds (VFTs) (single pulse scan of T-wave vulnerable period) were measured in normal (N) and in ischemic (I) (snare temporarily closed) hearts of all dogs while standing at rest. One day later VFTs were redetermined for C dogs at rest and for E dogs during treadmill exercise (3.5 mph at 30% grade). Within and between group t-tests showed no statistically significant change in N VFTs or in C I VFTs. For 8 E dogs, exercise increased the drop in VFTs during coronary occlusion by 7.7 $\pm$ 6.7 ma (23%) ($p < 0.01$). In the remaining 5 E dogs, spontaneous VF occurred during the first 8 minutes of I exercise. The only occurrences of spontaneous VF were during I exercise. A separate group of 5 E dogs were studied 10-14 days after 6-hydroxydopamine sympathectomy (60 mg/kg I.V.). The effect of exercise on VF was similar to that described above. These data suggest that moderate dynamic exercise may greatly enhance the risk of ID during the onset of myocardial ischemia. In the normal heart, there was no indication that exercise can increase ID risk.

COMPARISON OF CHANGES IN R-WAVE AMPLITUDE (RWA) AND ST SEGMENTS IN TREADMILL STRESS TESTING (TST) AS A PREDICTOR OF CAD

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Coronary angiograms and treadmill stress tests were reviewed independently in 108 selected cases. There were 16 (15%) patients with infarcts on EKG. Changes in RWA and ST segments during exercise were noted and the sensitivity and specificity of each as a predictor of CAD were determined. A significant lesion was greater than 70% stenosis. ST segment changes had a sensitivity of 49%, and a specificity of 74%. RWA changes had a sensitivity of 68% and a specificity of 84%. If the infarcts were excluded the sensitivity increased to 55% in ST segment depression, and 78% for RWA changes, and 86% for the index. An index formed from the sum of the change in RWA and the magnitude of ST segment change yielded a sensitivity of 74% and a specificity of 78%. Of those patients with an RWA decrease, 69% had no CAD while 31% had significant lesions. Of those patients with an RWA increase or no change, 83% had CAD while 17% were normal. Of the 83% with CAD, 81% had two or three vessel disease while only 19% had single vessel disease. RWA increase or no change during TST is a more reliable indicator of significant CAD in our laboratory than ST segment changes.

MAXIMAL EXERCISE TESTING FOR THE DETECTION OF CORONARY DISEASE IN 2517 MALES (CASS)

Thomas J. Ryan, MD, FACC; Mary Jo Gillespie, MS; J. Ward Kennedy, MD, FACC; Michael Schloss, MD; Felix Tristani, MD, FACC; Michael B. Mock, MD, FACC; Thomas Killip, MD, FACC, Boston University Medical Center, Boston, MA, University of Washington, Seattle and Participating CASS Sites

Between July 1974 and Feb 1977 2517 males entered into the Collaborative Study on Coronary Artery Surgery (CASS) had an exercise treadmill test (ETT) by a modified Bruce protocol in conjunction with coronary arteriography. ST segment depression or elevation $\geq$1.0 mm was considered a +ETT. Coronary disease (CAD), defined as $\geq$70% stenosis in at least one major vessel, was present in 2019 (80%). ETT had a sensitivity of 52% and specificity of 83%. Of 982 pts with no Hx or ECG evidence of infarction (MI), 665 were judged to have coronary pain (AP). In the 52% (347/665) with +ETT, 324 (93%) had CAD and 240 (69%) had multi-vessel disease (MVD). Among the 318 men with AP and -ETT, 189 (59%) had CAD and 101 (32%) had MVD. Among the 187 men with pain judged not to be AP (NAP), 41 had +ETT but only 44% (18/41) had CAD and 15% (6/41) had MVD. Of the 146 men with NAP and -ETT, 21 (14%) had CAD and 4 (3%) had MVD. Prior MI occurred in 1535 pts, among whom MVD was present in 80% (556/697) with +ETT compared to 57% (474/838) with -ETT ($p<0.001$).

We conclude: 1) a positive stress test in males without prior MI increases the likelihood of CAD and MVD; 2) a negative test is helpful only in excluding MVD in males with atypical chest pain and 3) males with prior MI and a positive test are likely to have MVD.

REPRODUCIBILITY OF SERIAL EXERCISE TESTS IN THE EVALUATION OF FUNCTIONAL CAPACITY AND MYOCARDIAL ISCHEMIA

Garrett Lee, MD; Roy Kaku, MD; Dean T. Mason, MD, FACC; Ezra A. Amsterdam, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis, California.

Although exercise tests (ET) are often used to evaluate therapy and follow-up of patients (pts) with coronary disease (CAD), little data are available regarding reproducibility of serial ET. Thus, 84 ET were performed in 17 pts with angiographically documented CAD and myocardial ischemia (>1mm ST depression) on ET electrocardiogram. No pts manifested valvular disease or used cardiac drugs. After an instructional stress test, ET were performed according to the Bruce protocol to an end-point of moderate (3+ of 4+) angina before (C) and after 0.6 mg nitroglycerin (NTG). This procedure was repeated in one month. Compared to C of initial testing, values for C after one month were similar; exercise duration (DUR) (302→306 sec), maximal oxygen consumption (VO_2) (21.1→21.3 cc/Kg/min), heart rate-blood pressure product (RPP) (23.3→21.6x10^3), and ST depression (ST) (2.1→2.1 mm); $p>.05$. Importantly, magnitude of NTG induced improvement was identical in initial and one month ET: DUR (88 vs 62 sec); VO_2 (3.4 vs 2.4 cc/Kg/min); ST (.8 vs .8 mm) (all $p>.05$). NTG did not change RPP. Thus, these data indicate that exercise performance and ST depression are reproducible prior to and following NTG in CAD. Thereby serial ET can be utilized as a reliable quantitative measure of alterations in functional capacity and myocardial ischemia.

EXERCISE-INDUCED VENTRICULAR TACHYCARDIA: PREDICTION OF CHRONIC AMBULATORY VENTRICULAR ARRHYTHMIAS AND LACK OF CORRELATION WITH CARDIAC DISEASE AND PROGNOSIS

David M. Mokotoff,MD,Soraya Nouri,MD,MRCP,Miguel A. Quinones,MD,FACC,Gay K. McAllister,RCT,Don W. Chapman,MD, FACC,Richard R.Miller, MD,FACC, Baylor College of Medicine, Houston, Texas

Despite widespread application of maximal treadmill stress testing(TST), data are sparse concerning the significance of exercise-induced ventricular tachycardia (VT), defined as 3 or more successive ventricular ectopic beats (VEB) occurring during, or immediately following exercise.Prior reports suggest a relation between TST-induced VT, severe coronary artery disease(CAD), and poor prognosis. To evaluate this issue in a larger number of patients (pts), 19 pts, mean age 53(28-68)years,17/19 males, who developed VT with TST had 24 hour ambulatory monitoring (AM). Ten of the 19 had CAD, 2 nonischemic cardiomyopathy and 7 no evidence of heart disease. With TST,11/19 pts had sustained VT, 13/19 pts developed VT before achieving 90% maximal predicted heart rate,14/19 pts had VT during exercise, while 5/19 developed VT after stopping TST.Three of these latter 5 pts were normal while 2 had CAD.During ambulatory monitoring, VT occurred in 3/19(15%) of pts. 10 others(53%)had advanced VEB defined as $\geq$ 1 of following: couplets, bigeminy,VEB >10% total beats. Only 2 pts had no VEB with AM and neither had heart disease. With 1 to 52 months follow up (average 22.4)after index TST, 17/17 pts are alive.Two pts were lost to follow up. In conclusion, these data indicate that pts with treadmill exercise-induced ventricular tachycardia often have no cardiac disease. Further,exercise-induced VT does not presage sudden death in 22 month follow up even in pts with coronary disease. However,TST-VT does predict the presence of chronic advanced VEBs or VT in 68% of pts.

CORRELATION OF FLUOROSCOPICALLY DETECTED CORONARY ARTERY CALCIFICATION WITH EXERCISE ELECTROCARDIOGRAPHY IN ASYMPTOMATIC MEN

Michael J. Kelley, M.D., FACC; Edwin K. Huang, M.D.; Larry S. Cohen, M.D., FACC; Rene A. Langou, M.D.; Yale University School of Medicine, New Haven, Ct.

The presence of fluoroscopically detected coronary artery calcification (CAC) has been used as a method of assessing arteriosclerotic heart disease in symptomatic populations but has never been used for the detection of latent ischemic heart disease in the asymptomatic population. Therefore, we evaluated 129 healty males (average age 49 $\pm$ 6) with cardiac fluoroscopy followed by a submaximal exercise electrocardiogram (SEE). Of the 108 subjects who completed the SEE, 37 (34%) had calcification of at least 1 coronary artery. Sixteen of the 108 persons had a positive SEE. Of these 16, 13 (81%) had at least 1 CAC. Conversely, 13 of 37 (35%) with CAC had a positive SEE. A person with CAC had a ninefold increase in risk of having a positive SEE as opposed to one without CAC ($P<.00001$). The location of a calcific deposit conferred a greater risk for exercise induced ischemic changes. Forty-seven percent of individuals with CAC in the left anterior descending coronary artery had an abnormal exercise ECG as opposed to 33% and 16% of persons with circumflex and right coronary calcifications respectively. In evaluating the clinical profiles of all subjects, we found a significant correlation between CAC and the presence of systemic hypertension and coffee consumption.

We conclude that CAC discovered by cardiac fluoroscopy is an important predictor of those persons at risk for having an abnormal exercise electrocardiogram and possible preclinical ischemic heart disease.

THE ASSOCIATION OF FALSE-POSITIVE ST-T WAVE CHANGES SECONDARY TO HYPERVENTILATION AND MITRAL VALVE PROLAPSE

Julius M. Gardin, MD; Jeffrey M. Isner, MD; James A. Ronan Jr., MD, FACC; Samuel M. Fox III, MD, FACC; Georgetown University Hospital, Washington, D.C.

The occurence of ischemic-appearing ST-T wave changes with hyperventilation in patients (pts) who have no evidence of coronary artery disease has been previously reported, but its etiology is not well defined. To further investigate the basis of such a response, the records of 1,678 consecutive patients undergoing treadmill exercise testing for routine indications and 90 seconds of forced hyperventilation (FH) were reviewed for a positive response to hyperventilation (PH). PH was defined as the presence at 80 msec following the J point of either (1) at least 0.1mV of flat or downsloping ST segment depression, or (2) at least 0.2 mV ST depression in patients with an upsloping ST segment. Twenty-eight patients (2%) fulfilled the criteria for PH. Follow-up was obtained in 21 of these patients (5 men and 16 women), all of whom underwent cardiac history, physical examination, echocardiography, and/or left ventriculography. Of this group, sixteen (76%) had evidence of mitral valve prolapse (MVP): fifteen were women. Six had MVP by auscultation alone, two by echo alone, two by angiography alone and six by a combination of studies. In the five case (24%) in which the diagnosis of MVP could not be established, complete evaluation by all the above diagnostic modalities had not been possible. FH performed in another random group of fifteen patients with MVP revealed PH in only one (7%). We conclude that (1) the occurence of PH is relatively uncommon; and (2) PH in women has a high predictive value (94%) for the presence of MVP, but is not a sensitive marker.

ABNORMAL BLOOD PRESSURE RESPONSE AND MARKED ISCHEMIC ST CHANGES WITH EXERCISE AS PREDICTORS OF SEVERE CORONARY DISEASE.

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Abnormal blood pressure response (AbBP) and marked ST depression (MIST) with exercise are presumed indicators of severe coronary disease. AbBP was defined as the failure of BP to rise or > 20 mmHg fall in the absence of antihypertensive medication and MIST was defined as $\geq$ 0.3 mv ST depression in absence of digitalis. These parameters were correlated with the severity of coronary artery disease (>70% stenosis). Of 306 patients (pts) who underwent maximal treadmill test prior to cardiac catheterization, 103 met one or both criteria. The results follow:

# vessels	0	1	2	3	Left Main
# patients	50	51	65	116	24
AbBP only	3	4	8	20	9
MIST only	1	2	6	16	6
Both	0	0	3	16	9
Total	4	6	17	52	24

AbBP has a sensitivity of 38% and a specificity of 90% for pts with 3 vessel disease (3VD) or Left Main (LtMn). The sensitivity rises to 54% when pts with MIST are included. For LtMn disease AbBP has a sensitivity of 75% and a specificity of 81%. If pts with MIST are included the sensitivity is 100%.

In summary, an AbBP response to exercise is a sensitive predictor of severe coronary disease and quite specific for 3VD or LtMn; AbBP has a greater sensitivity than a marked ischemic ST response as defined above and is particularly important when ST segments cannot be evaluated because of drugs or conduction abnormality.

ABILITY OF R-WAVE AMPLITUDE (RWA) CHANGES TO REDUCE FALSE NEGATIVE (FN) AND FALSE POSITIVE (FP) RESPONSES BY ST DEPRESSION IN TREADMILL STRESS TESTING (TST)

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A group of 159 patients were randomly selected by computer who were FP (52) and FN (107) on TST by ST segment changes. The coronary angiograms were reviewed in all cases and were the basis in determining that a TST was FP or FN. Significant coronary artery disease (CAD) was defined as greater than 70% stenosis. RWA changes were measured in the control and immediate post exercise periods. An increase or no change in RWA in the immediate post exercise period was taken as evidence of significant CAD and a decrease in RWA was taken as evidence of insignificant CAD or normal response. An index was made from the sum of the ST segment and RWA changes. A positive index or 0 value was evidence of significant CAD and a negative value was insignificant or no CAD. The RWA changes reduced the FP group by 37 (71%) while the index reduced the FP group by 31 (60%). The RWA changes reduced the FN group by 47 (53%) while the index reduced the FN group by 62 (58%). If the 64 infarcts were excluded, 25 (58%) of the 43 were correctly evaluated by RWA changes while 29 (67%) were correctly identified by the index. RWA changes can significantly reduce the incidence of FP and FN tests during TSTing. ST segment depression with RWA decrease suggests a FP test or single vessel disease while RWA increase without significant ST depression suggests a false negative test.

EXERCISE STRESS TESTING IN PATIENTS WITH ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES: SIMILAR FREQUENCY OF FALSE POSITIVE ISCHEMIC RESPONSES IN MALES AND FEMALES

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It is widely believed that the frequency of false positive responses for ischemia during exercise electrocardiography is significantly higher in females than males. To assess the validity of this concept, exercise electrocardiograms and coronary arteriography were compared in 96 male and 65 female patients. All patients had normal coronary arteries and no evidence of cardiac disease as documented by cardiac catheterization and selective coronary arteriography. There was no significant difference ($p>.05$) in age between the two groups (males - mean age 47 yrs, range 20-69 yrs; females - mean age 50 yrs, range 21-68 yrs). All patients underwent symptom-limited, maximal treadmill exercise tests. Ischemic response on exercise electrocardiogram was defined as horizontal ST segment depression of $\geq$1 mm for $\geq$60 msec. Ischemic electrocardiographic response occurred in 15% (10/65) of females compared to 11% (11/96) of males ($p>.05$). However, chest pain was associated with ischemic exercise response in 6/10 (60%) females and 2/11 (18%) males ($p<.05$). Although the combination of ischemic ST response and chest pain during exercise stress testing may be more common in females than males in the presence of normal coronary arteries, the overall frequency of ischemic exercise electrocardiograms is not significantly different in males and females with normal coronary arteries.

TUESDAY, MARCH 7, 1978
PM
NUCLEAR CARDIOLOGY
2:00 to 5:30

EXTERNAL QUANTIFICATION OF MYOCARDIAL METABOLISM WITH ^{11}C-LABELED FATTY ACIDS

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Decreased accumulation of ^{11}C-palmitate with ischemia, demonstrated initially in isolated perfused hearts, permitted quantification of myocardial infarction in man by positron emission transaxial tomography. To determine whether external detection of the rate of metabolism of incorporated physiological substrates is also possible, we studied isovolumic rabbit hearts (n=7) equilibrated at 15 ml/min with oxygenated Krebs-Henseleit solution containing 0.4 mM albumin, 0.4 mM palmitate, and 70 μU/ml of insulin. Ventricular rate was maintained constant by pacing after the SA node was crushed. ^{11}C-palmitate (50 μCi) was then injected as a bolus into the perfusate. Determinants of cardiac work were selectively altered during an eight minute interval after extracellular tracer had been washed out, and positron emission from the heart was measured with two NaI (Tl) crystals and quantified by computer. At constant heart rate, elevations of left ventricular diastolic pressure (n=3), from 1 to 20 mm Hg produced a 1.5 to 3 fold increase in the rate of clearance of intracellular counts compared to control conditions in the same hearts. With pressure constant, acceleration of heart rate from 90 to 220 beats/min (n=2) increased clearance rates by twofold. With cardioplegia induced by KCl, clearance virtually ceased (n=2). Paired ventricular pacing (n=4), utilized to augment metabolism substantially, increased the rate of clearance by 3 to 5 fold, ($p < .01$). External detection of these marked changes in metabolism suggests that positron emission transaxial tomography is applicable to assessment of regional metabolism in vivo as well.

MYOCARDIAL PERFUSION IMAGING DURING PHARMACOLOGIC CORONARY VASODILATATION IN ASSESSING CORONARY DISEASE

Peter C. Albro MD; K. Lance Gould MD, FACC; R. Jeffrey Westcott MD, Glen W. Hamilton MD. VA Hospital, Seattle,WA.

In order to determine whether pharmacologic coronary vasodilatation is an adequate substitute for exercise (E) stress, ^{201}Tl myocardial imaging was performed at rest, during maximal treadmill exercise and during coronary artery vasodilatation induced by intravenous dipyridamole in 42 patients (pts) undergoing coronary angiography. Dipyridamole (D) (0.142 mg/kg/min.) was infused for 4 minutes with blood pressure (BP) and ECG monitoring. 4 minutes after infusion, ^{201}Tl was given intravenously with pts standing, walking in place. Myocardial/background (M/B) count ratios of 2.3 $\pm$ 0.5 were significantly higher than M/B ratios for E images (2.1 $\pm$ 0.4; $p < 0.02$). Abnormalities were identified in 21/31 (68%) of E and D images in pts with > 50% stenosis of one or more coronary arteries. 13/31 (42%) had abnormal resting images; in 9 pts image defects increased with E (8/9) or D (9/9). 1/11 pts with no stenosis $\geq$ 50% had defects on D and E images and 1/11 had a defect with E only.

Following D infusion BP decreased from 130$\pm$14/81$\pm$10 supine to 121$\pm$18/73$\pm$10 standing ($p < .001$). M/B ratios in D images increased compared to rest, and these increases were significantly greater in pts with larger increments in HR, suggesting individual variation in drug effect at this fixed dosage. 12 pts (29%) had mild angina. 2 pts (5%) had gradual onset of significant angina, terminated by intravenous aminophylline, an antagonist of D, after ^{201}Tl injection.

Intravenous infusion of dipyridamole is a safe, effective means of inducing coronary vasodilatation in order to identify regional perfusion abnormalities without exercise stress in pts with coronary artery disease.

IMPROVED DIAGNOSTIC ACCURACY OF TOMOGRAPHIC MYOCARDIAL PERFUSION SCINTIGRAPHY USING AN ANGER CAMERA

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A new method of planar emission tomography was developed using a standard wide field Anger scintillation camera, a seven pinhole collimator, and a computer algorithm. Eleven planes at 0.8 cm separation are reconstructed from a single projection scintigram. Planar resolution (full-width-half-maximum) of the method is 1.0 cm and depth resolution is 1.5 cm. Twenty-four patients, 11 without and 13 with angiographically demonstrated coronary artery stenosis (≥ 70%) underwent graded treadmill (Bruce protocol) electrocardiography (ECG) and stress thallium-201 scintigraphy using both the tomographic (TOMO) and standard parallel hole collimation (NON-TOMO) techniques. TOMO required approximately 600 seconds to acquire 750,000 counts following 1.5 mCi thallium injection. One patient with coronary artery disease did not achieve either 85% maximum heart rate or 1 mm ST segment horizontal depression (positive ECG). Of the 11 normal individuals, 2 had positive ECG, and none had abnormal TOMO or NON-TOMO. Of the 13 patients with coronary artery disease with adequate stress testing, 7 had positive ECG, 9 had abnormal NON-TOMO, and 12 had abnormal TOMO, defined as > 50% reduction in regional wall count density. Initial results suggest that myocardial perfusion scintigraphy is more sensitive and selective to the presence of coronary artery disease than stress electrocardiography, and that multi-pinhole Anger camera tomography correlates significantly better with angiography than does non-tomographic scintigraphy ($P<.05$).

USEFULLNESS AND LIMITATIONS OF RESTING THALLIUM-201 SCINTIGRAPHY IN DETECTING LOCATION AND SIZE OF MYOCARDIAL INFARCTION.

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To evaluate the accuracy of Thallium-201 (Tl) scintigraphy in determining myocardial infarct (MI) size and location, biplane (AP/lateral) resting Tl scans, biplane (AP lateral) left ventricular (LV) angiograms, and EKG were compared in 32 patients (pts) at 7±3 mos post-MI. Angiograms and Tl scans were made 6±2 days apart. Angiographic LV asynergy was quantified as % abnormally contracting segment (ACS)--the akinetic or dyskinetic fraction of end-diastolic LV circumference; Tl defect was quantified as the ratio of area of Tl defect to area of total potential Tl uptake. Of pts having ACS >6%, 91% (20/22) had positive Tl scans, while only 40% (4/10) of pts with ACS ≤6% had positive Tl scans ($p<.01$). The Tl defect location correlated with EKG in 24/32 (75%) while ACS location correlated with EKG in 23/32 (72%). Of the pts with ACS > 6%, 29/32 (91%) Tl scan sites showed no major disagreement when compared to ACS location. Of 6 pts with ACS and no Tl defect, 4/6 had ACS ≤6% and 5/6 had normal EKG. There were 2/32 (7%) false positive Tl scans (normal EKG & no ACS) and both were inferoapical defects. The %ACS correlated highly with Tl defect size ($r=.80$). Separate AP & lateral Tl defect size correlated less well with respective angiographic views (AP, $r=.79$/lateral, $r=.67$). Ejection fraction correlated with % Tl defect ($r=.60$).

Thus, in post-MI pts, Thallium-201 scintigraphy accurately indicates the presence, location, and size of scar as assessed independently by angiogram and/or EKG. Limitations include a reduced qualitative and quantitative accuracy in pts having small inferoapical Tl defects and/or angiographic scar size ≤6%.

OBSTRUCTIVE VS NONOBSTRUCTIVE ASYMMETRIC SEPTAL HYPERTROPHY: DIFFERENCES IN LEFT VENTRICULAR FUNCTION WITH EXERCISE

Jeffrey S. Borer, MD; Stephen L. Bacharach, PhD; Michael V. Green, MS; Kenneth M. Kent, MD, PhD; Barry J. Maron, MD; Douglas R. Rosing, MD; Stuart F. Seides, MD, FACC; Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

Morphologic studies indicate that the cardiomyopathy present in all pts with asymmetric septal hypertrophy (ASH) may be more extensive in pts without obstruction (obs). Therefore, LV systolic function (SF) might be more affected in this subgroup. However, pts with ASH usually have supernormal LVSF (evidenced by cavity obliteration on angio) even in the presence of congestive symptoms. Hence, such symptoms are attributed to poor LV compliance. However, LVSF has not been assessed during stress. This point is critical since in other diseases systolic dysfunction may be detected only during stress. Therefore, we employed radionuclide cineangiography during exercise to study 63 pts with ASH (40 with and 23 without obs) and 30 normals. This count-based technique permits assessment of LV function during intense exercise and is not affected by irregular LV geometry. LV ejection fraction (EF) at rest was 57±1% in normals, and was significantly ($p<.01$) elevated both in pts with obs (76±2%) and in pts without obs (64±4%). While EF fell ($p<.01$) during maximal exercise in pts with obs (to 72±2%), it remained indistinguishable from normal (71±2%). In contrast, EF fell to 51±3% in pts without obs ($p<.001$ vs normal); though >70% in 3 pts, EF fell below 55% (lowest normal value) in 11 of 23 pts. Thus, although EF at rest is above normal in pts with ASH whether or not obs is present, many pts without obs manifest depressed EF during exercise. This raises the possibility that symptomatic pts without obs might benefit from inotropic therapy to support systolic function during exertion.

TIME COURSE AND MECHANISM OF RESOLUTION OF THALLIUM-201 DEFECTS AFTER TRANSIENT MYOCARDIAL ISCHEMIA

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Resolution of myocardial defects in patients has been demonstrated by serial imaging after a single dose of ^{201}Tl administered during exercise-induced ischemia or spontaneous angina. Disappearance of defects in ^{201}Tl uptake over time may be related to: (a)different rates of tracer washout from normal (N) and ischemic (IS) myocardium or (b) active ^{201}Tl redistribution into IS zones. To determine which of these mechanisms are operant, 17 anesthetized dogs received a single dose of 1.5 mCi of ^{201}Tl IV 10 min after occlusion (occl) of the left anterior descending coronary artery. Coronary flow was restored 10 min after ^{201}Tl administration Transmural specimens were obtained in situ from N (mean weight 28±1mg [SEM]) and IS (19±.4mg) regions with a biopsy drill during occl and 5 min (n=4), 20 min (n=8), and 4 hr (n=5) after ^{201}Tl administration. ^{201}Tl activity (counts/10 min/mg) was 14±6% of N activity in the IS zone during occl and increased to 25±5% ($p<.05$) in dogs undergoing 5 min of reperfusion (RP). In dogs undergoing 20 min of RP, ^{201}Tl activity increased from 12±3% of N activity during occl to 43±6% ($p<.001$) after RP. In the 4 hr RP group, ^{201}Tl activity in the IS zone increased from 19±4% during occl to 77±6% ($p<.001$) after RP. In this group, ^{201}Tl activity in the N zone decreased by only 33±5% during the 4 hrs of RP, representing ^{201}Tl washout. These data indicate (1) when ^{201}Tl is administered during transient coronary occlusion in dogs, near equalization of activity between normal and ischemic zones occurs by 4 hrs and (2) this near equalization is related to both redistribution of ^{201}Tl into ischemic areas and to ^{201}Tl washout from normal areas, with redistribution predominating.

BENEFIT OF THALLIUM 201 MYOCARDIAL PERFUSION STUDIES IN NEONATES

David L. Gilday, M.D., F.R.C.P. (C); Robert Howman-Giles, M.D.; Richard Rowe, M.D., F.R.C.P. (C); The Hospital for Sick Children, Toronto, Ontario

Newborn infants who present with symptoms of myocardial failure are often difficult to categorize. The diagnosis of intrinsic myocardial disease has always been one of exclusion. The global ischemia of "Transient Myocardial Ischemia" and focal ischemia secondary to an aberrant left coronary artery (ALCA) can now be readily diagnosed by Thallium-201 (TL201) myocardial imaging. We have examined 24 neonates, with 1.15 millicuries of Thallium-201 citrate/m2 body surface area, using a high resolution gamma camera and a converging collimator.

Little identifiable myocardial concentration of TL201 was found in 13 babies with global ischemia (heart to lung ratios averaged 1.3) and improved dramatically with time (ratios greater than 2.1). Focal ischemia was detected in 4 newborn babies (3 aortic stenoses with coarctation and 1 ALCA). Myocardial hypertrophy was easily recognized in 8 neonates (3 had defects as well) as was cardiac dilatation (ALCA). These all had normal concentration of TL201 in the myocardium.

Two full term babies had normal scans.

TL201 myocardial imaging has extended the range of cardiological investigation inthe newborn by permitting direct visualization of the myocardial perfusion for the first time. Although the radiation dose to the target organ, the kidneys, is higher than other tracer studies, the risk if any is considered acceptable in view of the benefit achieved.

THALLIUM-201 STRESS MYOCARDIAL SCINTIGRAPHY: APPLICATION IN ASYMPTOMATIC PATIENTS WITH POSITIVE EXERCISE ELECTROCARDIOGRAMS. Daniel S. Berman, M.D., F.A.C.C.; Ezra A. Amsterdam, M.D., F.A.C.C.; James A. Jove, M.D.; Edwin Glass, M.D.; Donald Levene, M.D.; Gerald L. DeNardo, M.D.; and Dean T. Mason, M.D., F.A.C.C. Cedars-Sinai Medical Center, Los Angeles, Ca and UC Davis, California

With wider use of exercise (Ex) ECG in asymptomatic patients (pts), the proportion of pts with false positive stress ECG has increased dramatically. To determine whether thallium-201 (Tl-201) Ex myocardial scintigraphy (Sc) is useful in this group, treadmill Ex and equilibrium (Eq) Tl-201 Sc was performed in 21 pts undergoing diagnostic coronary arteriography (CA). In each pt, prior stress ECG was positive (greater than 1 mm ST depression with resting isoelectric ST). Ex Sc was performed with a 37 tube camera in 4 views. If Ex Sc was normal (Nl), no additional Sc was performed. If Ex Sc was abnormal, Sc was repeated 4 hours after Ex (Eq Sc). Eq images replaced resting Sc. Sc was interpreted without knowledge of CA results. On CA, >75% stenosis was called significant hemodynamic obstruction. With no lesions, or if narrowing was less than 40%, pts were classified as Nl CA. No pts had between 40-75% narrowing alone without >75% stenosis in a major coronary artery. Of the 21 pts, 14 had Nl CA and 7 pts had coronary artery disease (CAD):four had 1 vessel, one had 2 vessel, and two had 3 vessel CAD. In all 14 pts with Nl CA, Tl-201 Ex Sc was Nl. Six of the 7 CAD pts had focal abnormalities in Tl-201 Ex Sc with Nl Eq Sc. The remaining pt with Nl Tl-201 Sc had 1 vessel CAD. The results suggest that Tl-201 Ex and Eq Sc accurately separates asymptomatic pts with positive stress ECG into those with and those without CAD, thereby providing a potential basis for management of this group.

TRANSIENT DEFECTS ON RESTING THALLIUM SCANS IN PATIENTS WITH CORONARY ARTERY DISEASE

Henry Gewirtz, MD; George A. Beller, MD; H. William Strauss, MD; Robert E. Dinsmore, MD, FACC; Kenneth A. McKusick, MD; Leonard M. Zir, MD; Gerald M. Pohost, MD, FACC, Massachusetts General Hospital, Boston, MA

Defects on resting Thallium-201 (Tl) scans in patients who do not have evidence of acute myocardial ischemia are thought to represent myocardial scar. The significance of the resting defect was studied in 14 patients (pts) with stable but severe coronary artery disease (CAD). Serial imaging was performed in 2 or 3 views within 10 minutes of administration of 1.5 mCi of Tl and repeated over a 2 to 4 hour period. Images were divided into 3 zones in the anterior and 3 in the left anterior oblique view. Thirteen of 14 pts had at least 1 well-defined defect on the initial scan, but only 6 had ECG evidence of myocardial scar (MS). An initial scan defect was present in 38/84 zones; on later scans 18 defects persisted while 20 filled-in. Nine of these persistent defects in 5 pts were associated with ECG signs of MS. Only 1 transient defect (Td) was seen in an area corresponding to a region of MS on ECG. However, 19/20 Td's were found in the distribution of severe CAD. Further, in 15 zones with Td (9 pts) analysis of corresponding angiographic LV wall motion revealed 11 associated with normal wall motion, 3 with hypokinesia and 1 with akinesia. Only 1 zone associated with normal wall motion and subcritical (<50% stenosis) CAD had a Td on scan.

Thus, 1) in patients with stable CAD initial resting defects on Tl scans do not necessarily indicate myocardial scar, 2) many of these defects fill-in if imaged serially and 3) Td's are almost always associated with severe CAD but normal or only mildly abnormal LV wall motion.

SERIAL CHANGES IN SCINTIGRAPHIC MEASURES OF ISCHEMIA AND INFARCTION AND IN LEFT VENTRICULAR FUNCTION FOLLOWING CORONARY OCCLUSION IN DOGS.

G.A. Misbach, MD; E.H. Botvinick, MD; D.M. Shames, MD; J.V. Tyberg, MD, PhD; W.W. Parmley, MD, FACC; University of California, San Francisco, California.

We sought to evaluate temporal scintigraphic and functional changes after infarction. After closed chest placement of occlusive plugs in coronary arteries of 13 dogs, we performed serial Tl-201 scans and cineventriculograms, as survival permitted, to a maximum of 5 weeks, and Tc99m pyrophosphate (PYP) images in survivors (10 dogs) at 48 hours. Nitro-blue tetrazolium (NBT) measured histologic infarct size (IS).

PYP was abnormal in 7 dogs, the same 7 with NBT infarcts (3-23 gm). PYP IS correlated with NBT IS (r=.90, p<.01). In 6/7 infarcted dogs with early Tl-201 defects, defect size did not correlate with NBT IS. Of 3 dogs without PYP and NBT infarct, 1 had early Tl-201 defect and 2 had wall motion abnormalities (WMA). Of 13 dogs, 12 had early WMA, but only 9 had Tl-201 defects. Ejection fraction and segmental WMA in the left lateral view correlated significantly with NBT and PYP IS and improved with time. Tl-201 defects in infarcted dogs showed obvious temporal improvement in 5/6 dogs. Biopsy of infarct scars showed Tl-201 counts/mg as high as 66% of that in normal myocardium. Dense inflammation over infarct scar in 1 dog had Tl-201 counts/mg 30% of normal. WMA remained severe despite dramatic temporal reduction in Tl-201 defect size.

We conclude: (1) in addition to reperfusion of ischemic myocardium, serial reduction of Tl-201 defects may reflect perfusion of organizing infarct scar or perfusion of superimposed tissues; (2) WMA are more sensitive to ischemia than Tl-201 and correlate with infarct size; (3) WMA remained severe despite dramatic reduction in Tl-201 defect size.

THE FUNCTIONAL SIGNIFICANCE OF CORONARY COLLATERALS.
Pierre Rigo, MD, Lewis C. Becker, MD, FACC, Lawrence C. Griffith, MD, FACC, Philip O. Alderson, MD, Henry N. Wagner, Jr, MD. Johns Hopkins University, Baltimore, Md.

Although coronary collaterals are commonly seen in patients (pts) with coronary artery disease (CAD), it is uncertain whether they are effective in protecting the myocardium from ischemia during exercise. In this study we used segmental analysis of Thallium-201 (TL) perfusion imaging at rest and after exercise to look for direct evidence of collateral protection. Of 154 consecutive pts with CAD having coronary angiography and TL rest/exercise imaging, 30 pts were selected who had at least 2 vascular areas at risk for ischemia (> 50% stenosis in LAD, RCA, and/or LCX) and who developed a new TL perfusion defect in one or more of these areas. Seventeen vascular areas (in 13 pts) were perfused by angiographically visualized collaterals in the absence of historical, ECG, or angiographic evidence of myocardial infarction. Ten of these areas, despite 100% obstruction of the corresponding vessel, did not become abnormal with exercise even though other areas of the heart developed perfusion defects. These 10 areas were therefore protected by coronary collaterals. Seven of the 17 areas developed defects and were not protected. In contrast, in 8 pts without angiographically visible collaterals, the region fed by the most severely obstructed vessel always developed a defect (Yates corrected $X^2 = 5.58$, $p < 0.025$). In 13 pts collaterals were visualized to previously infarcted vascular areas, but in each case that area developed either a new (9 pts) or larger (4 pts) TL defect, indicating lack of protection. The findings suggest that coronary collaterals visualized by angiography can offer at least relative protection from exercise-induced ischemia if they supply a non-infarcted region of myocardium.

ACCURACY OF NONINVASIVELY DETERMINED LEFT VENTRICULAR VOLUMES BY GATED RADIONUCLIDE CINEANGIOGRAPHY IN CORONARY, VALVULAR AND MYOCARDIAL HEART DISEASES
Edwin C. Glass, MD; James A. Joye, MD; Daniel S. Berman, MD, FACC; Ezra A. Amsterdam, MD, FACC; Anthony N. DeMaria, MD, FACC; Gerald L. DeNardo, MD; Dean T. Mason, MD, FACC, University of California, Davis, California

Left ventricular volumes (LVV) were determined in 33 heart disease patients by direct measurement of biplane end-systolic and end-diastolic images from multiple gated blood pool scintigrams (MGBPA) using a computerized scintillation camera, 99m-Tc labelled red blood cells, and a correction factor based upon an image reference grid of known dimensions. LVV were calculated by the equation which represents the left ventricle as an ellipsoid, the dimensions of which were determined from the right anterior oblique (RAO) and left anterior oblique (LAO) views of the MGBPS. Left ventricular volumes determined by this technique showed good correlation ($r = .84$, $n = 46$) with volumes measured by single plane contrast angiography. Further, the radionuclide blood pool derived ejection fractions (EF) showed reasonable correlation with EF by catheterization ($r = .81$, $n = 25$) and with EF by computerized edge determination methods using MGBPS ($r = .91$, $n = 33$). LAO images were routinely obtained only from the center one-quarter of the scintillation crystal. LVV and EF from MGBPS using right anterior oblique views taken from the entire field of view showed closer correlation with LVV ($r = .90$, $n = 10$) and EF ($v = .90$, $n = 6$) by catheterization and with EF by computer from MGBPS ($r = .93$, $n = 13$), than when only the center one-quarter of the scintillation crystal was used for the RAO view. These findings demonstrate that noninvasive MGBPS is valuable in the assessment of cardiac function by determinations of LVV and EF, as well as by the generation of dynamic radionuclide cineangiograms of the left ventricular chamber.

TUESDAY, MARCH 7, 1978
PM
INVESTIGATION IN VALVULAR HEART DISEASE
2:00 to 5:30

PREVALENCE AND NATURE OF VENTRICULAR ECTOPY IN HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY: EVALUATION BY AMBULATORY MONITORING
Craig M. Pratt, MD; Robert D. Swenson, BS; James Price MD; Louis A. Vismara, MD, FACC; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis, California

Although sudden death may occur in hypertrophic obstructive cardiomyopathy (IHSS), little data are available regarding ventricular ectopy (VEA) in these patients (pts). Thus electrocardiography (ECG), treadmill exercise (ET) and 24 hour ambulatory monitoring (AM) were performed in 30 IHSS pts and compared to 39 normals (N). VEA was classified as simple (S) or complex (C)(bigeminy, multiform, repetitive). VEA and CVEA occurred more frequently in IHSS than N by AM: 73% vs 29% and 26% vs 3% respectively (both $p<.01$). VEA and CVEA were detected more frequently by AM than ET or standard ECG: VEA 73% vs 29% and 4% and CVEA 26% vs 9% and 0% respectively (all $p<.05$). Bradyarrhythmias were also more frequent by AM than ET or standard ECG: 16% vs 0% and 6% (both $p<.05$). To evaluate the mechanism of VEA, the relation of VEA to hemodynamics was analyzed:

	LVED	CI	RG	PG	MR
NO VEA	12	2.70	40	80	33
S VEA	15	3.25	40	73	38
C VEA	13	2.85	48	78	30

LVED=end-diastolic pressure, mm Hg; CI=cardiac index, $l/min/m^2$; RG=resting peak systolic gradient, mm Hg; PG=provoked peak systolic gradient, mm Hg; MR=mitral regurgitation; (all $p>.05$). Thus, ventricular ectopy is more common in IHSS than N, is best detected by ambulatory ECG monitoring, appears unrelated to abnormal hemodynamics, and may be a preventable cause of sudden death in IHSS.

EFFECTS OF SUCCESSFUL, UNCOMPLICATED VALVE REPLACEMENT ON VENTRICULAR HYPERTROPHY, VOLUME AND PERFORMANCE IN AORTIC STENOSIS AND IN AORTIC INCOMPETENCE
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Pre- and postoperative cardiac catheterization data from 10 patients with aortic stenosis (AS) and 8 with aortic incompetence (AI) with normal prosthetic function was analyzed.

In AS, left ventricular (LV) mass fell from 229±39 to 123±10 gm/m^2 ($p<0.05$); mean velocity of circumferential fiber shortening (mean Vcf) increased from 1.11±0.13 to 1.57±0.09 circ/sec ($p<0.025$); ejection fraction (EF) increased from 0.65±.05 to 0.76±.03 ($p<0.025$); LV end-diastolic pressure (EDP), peak equatorial wall stress (σE), LV end-diastolic volume index (EDVI), and cardiac index (CI) showed no significant change.

In AI, the LV mass fell from 222±18 to 128±17 gm/m^2 ($p<0.025$), LVEDVI from 205±22 to 140±24 ml/m^2 ($p<0.01$), and LVEDP from 22±2 to 10±2 mmHg ($p<0.005$). Mean Vcf was depressed both preoperatively 0.64±0.12 and postoperatively 0.80±0.14 circ/sec. σE, EF, and CI showed no significant change.

We conclude that myocardial hypertrophy with or without increased ventricular volume maintained adequate LV pump function preoperatively in AS and in AI. Preoperatively, ventricular performance (mean Vcf) was more depressed in AI than in AS. Following successful, uncomplicated valve replacement, ventricular volume and/or mass decreased substantially, but not to normal. Adequate LV pump function was maintained both in AS and in AI. Ventricular performance (mean Vcf) improved to normal in AS but remained depressed in AI.

LEFT VENTRICULAR FUNCTION IN AORTIC STENOSIS: RESPONSE TO EXERCISE AND EFFECTS OF OPERATION

Jeffrey S. Borer, MD; Stephen L. Bacharach, PhD; Michael V. Green, MS; Kenneth M. Kent, MD, PhD; Douglas R. Rosing, MD; Stuart F. Seides, MD, FACC, Charles L. McIntosh, MD, David Conkle, MD; Andrew G. Morrow, MD; Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

In pts with severe aortic stenosis (AS), pre-operative (op) clinical and hemodynamic assessment has not accurately predicted long-term prognosis after operation. However, such studies have been performed with the pt at rest. Study during the stress of exercise, by unmasking abnormalities in left ventricular function (LVF), might provide a more useful prognostic index, and also might permit accurate evaluation of the effects of operation on LVF. Therefore, we have utilized non-invasive radionuclide cineangiography to assess LVF during the stress of intense exercise. Twenty-eight pts with severe AS were studied. Prior to operation ejection fraction (EF) at rest was 68±3%, significantly greater than normal (57±1%, p<.001). During exercise preop, however, EF fell to 57±4% (nl 71±2%, p<.001). Moreover, during exercise all 30 normal subjects studied increased EF, and none had EF <55%; EF fell in 25 of the 28 pts with AS, and was <55% in 14. Exercise EF could not be predicted from rest EF, aortic valve area, gradient, or LVEDP. Thus far 12 pts have returned 6 mos postop. Postop EF at rest (67±5%) was unchanged, but during exercise it rose significantly from 56±7% to 72±3% (p<.05). We conclude that 1) while high normal EF is present at rest in most pts with severe AS, the stress of exercise causes a marked fall in EF in some pts, a finding of potentially prognostic importance. Moreover, 2) while operation often does not change the already supernormal EF at rest, it significantly improves EF response during exercise.

PHASIC CHANGE IN HUMAN CORONARY BLOOD FLOW WITH AORTIC INSUFFICIENCY.

John D. Folts, Ph. D, George G. Rowe, MD, FACC, Donald R. Kahn, M. D., George M. Kroncke, MD, William P. Young, MD. Depts. of Med. & Surg., Univ. Wisc., Madison, WI 53706.

We have previously shown that acute aortic insufficiency (AI) in chronically instrumented dogs produce a reverse in the normally high ratio of diastolic to systolic (D/S) coronary blood flow. Coronary flow with acute AI becomes high during systole and low during diastole, presumably due to the low diastolic pressures associated with AI. Right coronary blood flow was measured with an electromagnetic flowmeter in seven patients with severe AI and a dominant normal right coronary artery before and after surgical repair of the aortic valve. Before the valve was repaired the RCBF averaged 114 ± 32 ml/min and the D/S flow ratio averaged 0. 86 ± 0. 15. Mean arterial blood pressure (MABP) averaged 108 ± 18 mm Hg, heart rate 84 ± 19 beats/min, mean diastolic pressure averaged 70 ± 9 mm Hg. After the aortic valve was repaired with an average heart rate of 90 ± 15 and mean blood pressure of 105 ± 16 mm Hg the RCBF had increased to 170 ± 72 ml/min $p < 0.01$ with a D/S ratio of 2. 2 ± 0. 9 $p < 0.005$. Mean diastolic pressure averaged 84 mm Hg ± 16 after the valve was repaired. In all cases the RCBF increased after the valve was repaired. We postulate that the RCBF increased due to the improved diastolic perfusion pressure, and the change from predominantly systolic coronary flow to greater diastolic flow.

PREDICTORS OF LATE DEATHS DUE TO CONGESTIVE HEART FAILURE FOLLOWING OPERATION FOR AORTIC REGURGITATION

Robert O. Bonow, MD; Walter L. Henry, MD; Kenneth M.Kent, MD, PhD; Jeffrey S. Borer, MD; David R. Redwood, MD; David M. Conkle, MD; Charles L. McIntosh, MD; Andrew G. Morrow, MD; Stephen E. Epstein, MD, FACC; NHLBI, Bethesda, Md.

Many pts with successful aortic valve replacement (AVR) for symptomatic aortic regurgitation (AR) die from congestive heart failure (CHF) due to irreversible myocardial damage. Hence, if a preop predictor of poor postop risk could be identified before development of severe symptoms, earlier operation, with potential for enhanced postop survival, might be carried out. To determine whether any preop parameters accurately predict high risk of late postop death, preop data on 42 consecutive pts with AR surviving one month after isolated AVR were evaluated. 10 pts were followed for less than 1 yr. Of the remaining 32, 10 pts died late postop, and 22 were long term survivors (mean follow-up 3.3 yrs). 7 of 10 late postop deaths were related to CHF. Echo data showed that pts with late deaths due to CHF had lower preop ejection fractions (EF) than survivors (mean 46% vs 67%, p<.001). Late deaths related to CHF occurred in 0/12 pts with EF ≥64%, 2/9 with EF 54-63%, and 5/8 with EF <54%. LV end-systolic dimension (LVSD), but not end-diastolic dimension, was as powerful a predictor of late CHF death; 0/13 with LVSD ≤52mm, 3/9 with LVSD 53-60mm, and 4/7 with LVSD >60mm. 3 pts with late death unrelated to CHF (2 coronary-related and 1 sudden) all had EF >64% and LVSD <55. Other preop echo parameters as well as preop Estes ECG score, exercise testing, and hemodynamic data (pulmonary wedge, LV end-diastolic pressure and cardiac index) were not as predictive of late deaths due to CHF. We conclude that CHF due to LV dysfunction is the primary cause of late postop death following successful AVR for AR and that the population at risk can be identified preop by echocardiography.

PRE-LOAD REDUCTION IN MITRAL REGURGITATION: DETRIMENTAL HEMODYNAMIC EFFECTS

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In patients (PTS) with mitral regurgitation (MR) nitroprusside increases forward flow presumably by decreasing aortic impedance and reducing regurgitant flow. On the basis of this concept nitrates (NIT) have also been administered to PTS with MR. However, since the effect of NIT is predominantly preload rather than afterload reduction, regurgitant flow could increase. To test this hypothysis 7 PTS with isolated MR and no congestive symptoms underwent hemodynamic study and left ventricular angiography before and after 5-10 mg of chewable isosorbide dinitrate (ISDN).

	PCW	HR	AP	SVR	CO-F	CO-A	CO-R	EDVI	SVI-A	SVI-F	LC
Control	15	90	84	1461	4.3	8.6	4.4	126	61	31	0.6
ISDN	8	96	75	1643	3.7	9.1	5.2	113	58	25	0.6

PCW (Pulmonary capillary wedge in mm/Hg), HR (Heart rate), AP (Mean arterial pressure), SVR(systemic vascular resistance in dynes-sec-cm^{-5}), CO-F, A, R, (Cardiac output-Fick Angiographic, Regurgitant in liters/min), EDVI(End-diastolic volume index in cc/M^2), SVI-A, F (Stroke volume index-angiographic, Fick), LC (Left ventricular contractility index in gram-meters/M^2/min/EDVI).

ISDN produced a 47% drop in preload but a 12% increase in afterload. MR increased 18% while forward flow fell 14%. Contractility as assessed by LC was unchanged. Left ventricular systolic work per liter of CO-F actually increased minimally despite the fall in PCW (1.5 to 1.6 Kg-meters/M^2/min/CO-F). In the absence of congestive symptoms ISDN appears to offer no hemodynamic benefits and may actually worsen MR by favoring regurgitant flow.

BENEFICIAL EFFECTS OF HYDRALAZINE IN SEVERE MITRAL REGURGITATION. B.Massie MD; B.Greenberg MD; B.Brundage MD,FACC; K.Chatterjee MD, FACC; E.Botvinick MD; W.Parmley MD,FACC; University of California, San Francisco, California.

The reduction of impedance to forward left ventricular (LV) ejection should benefit patients (PTS) with mitral regurgitation (MR). Indeed, parenteral vasodilators which both lower systemic vascular resistance (SVR) and increase venous capacitance have proven effective acutely. We evaluated the response of 8 PTS with severe MR to hydralazine (H) which predominantly reduces LV afterload and can be employed chronically. Hemodynamic measurements and quantitative biplane LV angiography were performed pre- and 30 minutes post-intravenous H (0.3 mg/kg up to 20 mg). Oral H was continued for 48 hours in 4 PTS while regurgitant fraction (RF) and stroke volume index (SVI) were calculated from LV volumes determined by gated blood pool scintigraphy. Both acute and chronic administration of H significantly lowered SVR with a resultant increase in forward (F) SVI, reductions in R-SVI and RF, and fall in pulmonary capillary wedge (PCW) pressure. There were no significant changes in heart rate, LV end-diastolic volume or ejection fraction.

	BP	SVR	F-SVI	R-SVI	RF	PCW
Pre	99±6	2150±210	23±3	41±7	61±6%	30±4
Post	88±6*	1300±110**	34±3**	31±7*	42±8%**	23±3*
Chronic	89±5	980± 90*	43±6**	24±4*	36±5%**	19±5*

Both PTS maintained on H demonstrated marked symptomatic and radiographic improvement of congestive heart failure. Our results indicate that selective impedance reduction significantly diminishes MR with consequent marked hemodynamic improvement. H may therefore provide a useful temporary or chronic mode of medical therapy in PTS with severe MR in whom surgery should optimally be delayed or is not feasible.

* $p<.05$

** $p<.01$ or below

PREMATURE CLOSURE OF PROSTHETIC MITRAL VALVES DURING LATE DIASTOLE: A CONSEQUENCE OF GRAVITY

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Although suspected, evidence for the role of gravity (G) in premature closure (PC) of prosthetic mitral valves (PMV) in late diastole has not yet been provided. To determine the effect of G on PC we studied 12 patients (pts) with PMV (Cooley-Cutter) by means of simultaneous echocardiography and cinefluoroscopy. All pts were in atrial fibrillation and in all PC had been observed during routine examination. None had aortic incompetence. To obtain different orientation of the PMV in respect to G, recordings were made in the following positions (POS): 1) pts lying on left side, 2) on right side, 3) supine, 4) prone, 5) sitting upright. In POS 1-3 the atrial side of the valve was lower and in POS 4 and 5 higher than the ventricular side. Optimal visualization of the poppet and poppet excursions was achieved with the x-ray beam parallel to the plane of the valve ring.

PC occurred in all pts when in POS 1, 2 or 3. The interval between preceding R wave and onset of PC ranged from 670 to 1130 msec, mean±SD was 897±106. PC was never observed in any patient in POS 4 or 5, even with diastolic lengths far exceeding those that allowed PC to occur in POS 1-3. In the absence of hemodynamic changes that could result in directional changes of pressure and flow across the PMV, the occurrence of PC and the observed POS - dependence is readily explained by the effect of G, directing the poppet toward closure in POS 1-3 and maintaining the PMV open in position 4 and 5. Since valvular flow prevents PC, all factors that influence valvular flow will also influence the onset of PC. Examination of pts with PMV in the positions described will be helpful in differentiating valvular malfunction from G related phenomena.

FACTORS AFFECTING RECOVERY OF LEFT VENTRICULAR FUNCTION AFTER MITRAL VALVE SURGERY

Gerhard Schuler, MD; John Ross, Jr.,MD, FACC;Allen Johnson, MD,FACC; George Dennish, MD,USNR; Heinz Schelbert, MD; Gary Francis, MD MC USNR, FACC; Kirk Peterson, MD, FACC, University of California, San Diego, and Naval Regional Medical Center, San Diego, California

The mechanisms of reduced left ventricular (LV) function following valve replacement for mitral regurgitation (MR) are uncertain. Thus,we compared 15 patients (pts) with MR and 17 pts with mitral stenosis (MS) using echocardiography (E) and radionuclide angiography (RA)before (preop) and serially for 14 months following operation (postop). E-ejection fraction (EF[%])and RA-EF correlated closely (n=63,r=0.91). Average enddiastolic dimension (EDD[cm]) and LV wall cross sectional area (CSA[cm^2])were significantly higher in pts with MR preop. In MR, EF fell from a normal value preop (68±2 to 54±5% $p<0.01$);in MS EF was normal both pre- and postop (67±3 to 65±3%). Crossclamp time and other surgical factors did not differ significantly between MR and MS. Several subgroups were apparent in MR:In pts with little cardiomegaly (CM) and EF >65% (n=6,EDD 5.7±.2),EF fell only slightly (73±2 to 67±3%,$p<0.01$) and CSA became normal (20±1 to 18±1,p:n.s.). In pts with moderate CM (n=6,EDD 6.3±.1) and EF<65%, EF became abnormal postop (62±2 to 53±2%,$p<0.005$); however,CSA regressed to normal (30±3 to 21±1,$p<0.01$). In pts with marked CM (n=3,EDD 8.0±2) and EF<65, EF became grossly abnormal postop (59±2 to 28±3%,$p<0.05$) and CSA failed to regress (31±3 to 33±3). We conclude that in MR with moderate CM, hypertrophy and dilatation regress postop and reduction of LV function is mild. However, with MR and severe CM normal ejection is not restored postop, LV function is markedly impaired and hypertrophy with dilatation persists.

AN ECHOCARDIOGRAPHIC-PHYSIOLOGIC INDEX OF THE SEVERITY OF MITRAL STENOSIS

Rose Marie Robertson, M.D., David Robertson, M.D., and Gottlieb C. Friesinger, M.D., F.A.C.C., Vanderbilt University School of Medicine, Nashville, Tennessee.

While echocardiography is the most sensitive method available for detecting the presence of rheumatic mitral valve involvement, it is less useful in judging the severity of obstruction. We evaluated the severity of mitral stenosis (MS) by studying the effect of the Valsalva maneuver (VM), 40 mm Hg for 20 seconds, on the echocardiographic left atrial (LAD) and left ventricular dimension (LVD) in 15 patients (pts) with catheterization-documented MS who had never had cardiac surgery. VM in 10 controls produced a decrease in echo LAD of 39.7±4.2% (S.E.), in LVD of 11.6±2.1% (S.E.), and a ratio of change in LAD/change in LVD of 5.4±1.7 (S.E.). Eleven pts with mitral valve areas (MVA) $\leq 1.4cm^2$ had a markedly blunted LAD response to VM, with a decrease of only 8.8±1.3% ($p<0.001$ vs controls); the 4 pts with MVA$>1.4cm^2$ had a normal LAD response. The LVD response was greater in the pt group than in the controls, but this difference was not statistically significant. However, the ratio of change in LAD/change in LVD was significantly lower ($p<0.02$) in the pt group as a whole, and in 3 of 4 pts with mild MS. MVA correlated well with percent decrease in LAD ($r=.66$, $p<0.01$), while the correlations of other echo parameters with MVA were not significant: E-F slope ($r=.21$), mitral valve excursion ($r=.30$), and leaflet separation ($r=.50$). Thus, the LAD/LVD response is useful in separating pts with MS from normals, and the LAD response may be the most sensitive available M-mode echocardiographic predictor of the severity of obstruction.

RELATIONSHIP OF VEGETATIONS ON ECHOGRAM TO THE CLINICAL COURSE AND SYSTEMIC EMBOLI IN BACTERIAL ENDOCARDITIS

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Since vegetations occurring in infectious endocarditis have been suggested to correlate with valve destruction and subsequent embolization, we evaluated the relationship between vegetations on M-mode echogram with the clinical course and emboli in patients with bacterial endocarditis. The study group was comprised of 32 patients (pts): 13 with vegetations on echogram (VEG)(11 aortic, 2 mitral and aortic) and 19 pts (all aortic) without ultrasound evidence of vegetations (NO-VEG). All pts manifested the classic clinical features of endocarditis, and a causative organism was cultured from the blood in all cases. The prevalence of etiologic organisms was similar in both groups. Congestive heart failure was present on admission in 3 of 13 VEG pts, but no NO-VEG pts. The clinical course of the pts with VEG was progressive congestive failure refractory to digitalis and diuretics in all cases. Cardiac catheterization was performed within 2 months of admission and revealed 4+ aortic regurgitation in all VEG patients. The mean left ventricular filling pressure of the VEG group was 30 mm Hg, and 12 of 13 pts required aortic valve replacement within 3 months. Importantly, a systemic embolus was not sustained by any VEG pt. In contrast, only 2 of 19 NO-VEG pts developed congestive heart failure ($p<.01$) and both pts required aortic valve replacement. Thus, the presence of vegetations on echogram indicates extensive valve destruction and predicts the appearance of congestive heart failure in nearly all cases. However, pts with vegetations on echogram do not appear to be at increased risk of systemic emboli.

TUESDAY, MARCH 7, 1978
PM
ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY—II
2:00 to 5:30

TYPE AND PROGNOSIS OF INTRAHISIAN BLOCKS IN PATIENTS WITH ISCHEMIC HEART DISEASE.

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The prognosis and spectrum of intrahisian block in patients with ischemic heart disease were evaluated based on His bundle recordings during atrial pacing and on serial ECGs. Fifteen of 130 patients (11.5%) with bundle branch block (BBB) or AV block were found to have intrahisian blocks (IHB). IHB could be divided into three groups: (1) proximal His bundle (HB) block, including type II, 2:1, and 4:1; (2) mid HB block, including narrowly split H, widely split H (H-H 380 msec), splintered type H, type I, 2:1, 3:1, and alternate beat 2:1; (3) distal HB block, including 2:1, 3:1 with 4:3 A-H block, and type II. Both unidirectional and bidirectional blocks were observed, and IHB in all 3 groups were either bradycardia or tachycardia dependent. Type I block was rare (1 patient). "Classical" type II block in which sudden HB block occurred was seen in only 1 of 15 patients and was bradycardia-dependent. The most common types of IHB were fixed-ratio blocks of 2:1, 3:1, or 4:1. Four of 5 patients with IHB but without BBB developed complete AV block within 3 months, whereas only 2 of 10 patients with IHB with BBB followed a similar course in 3 years. Thus, more than 10% of patients with ischemic heart disease and AV block have IHB. These blocks are likely to be 2:1, 3:1, or 4:1. In this study rapid progression to complete AV block was common in patients with IHB but without BBB.

NONINVASIVE PULSED DOPPLER STUDY OF MITRAL BLOOD FLOW

Benoit Diebold, MD; Pierre Théroux, MD; Martial G. Bourassa, MD, FACC; Jean-Léon Guermonprez, MD; Alain Barbet, Pierre Péronneau, Montreal Heart Institute, Montreal, Quebec and Hôpital Broussais, Paris, France.

The potential value of pulsed Doppler for detecting mitral regurgitation (MR) and assessing the severity of mitral stenosis (MS) was studied. The systolic flow of MR was recorded by scanning the left atrium behind the aorta with the transducer in the left parasternal position. Of 57 consecutive pts thus screened, 47 had adequate recordings which were interpreted without knowledge of the clinical or angiographic findings. MR was diagnosed by Doppler in 2 of 15 pts without angiographic MR, 8 of 16 with mild MR, 5 of 6 with moderate MR and 9 of 10 with severe MR.

40 pts were examined for MS with the transducer at the apex and the sampling site close to the mitral orifice. In the 24 pts in sinus rhythm, 3 patterns of diastolic flow could be defined which were then compared to mid-diastolic gradients obtained at cardiac catheterization:

DOPPLER FLOW PATTERN	# PTS	GRADIENT (mmHg)	
smooth, bifid flow	11	0.2±0.2	$p<0.001$
turbulent, dome-like flow	7	9.7±1.5	
turbulent, ascending flow	6	18.7±3.1	$p<0.02$

In pts in atrial fibrillation, the mid-diastolic gradient was 9 mmHg or more in all 5 showing a sustained flow throughout long diastoles while it was 8 mmHg or less in 9 of the 11 pts with a flow curve terminating before end-diastole ($p<0.005$). We conclude that 1) significant MR can be accurately diagnosed by pulsed Doppler, with a lower sensitivity in mild MR; 2) the degree of MS can be accurately assessed in sinus rhythm but only estimated in pts with atrial fibrillation.

SIGNIFICANCE OF CHRONIC BIFASICULAR BLOCK WITHOUT APPARENT ORGANIC HEART DISEASE

Ramesh Dhingra, MD, FACC; S. Sridhar, MD; Richard Kehoe, MD; Pablo Denes, MD, FACC; Delon Wu, MD, FACC; Fernando Amat-y-Leon, MD, FACC; Christopher Wyndham, MD; Kenneth Rosen, MD, FACC; University of Illinois, Chicago, Ill.

The significance of chronic bifasicular block (BFB) without apparent organic heart disease is unknown. In this study, we report our experience in patients (pts) with "primary bifasicular block" (PBFB), as defined by the presence of chronic BFB, no historical or physical evidence of organic heart disease, and normal radiographic heart size. Out of 518 pts in our BFB clinic, 84 have been classified as having PBFB. These 84 pts were detected, studied and followed between 1/70 and 9/77. The group consisted of 74 pts with right bundle branch block (BBB) with left or right axis deviation, eight with left BBB and two with alternating BBB. There were 69 males and 15 females with ages from 19 to 93 years (mean ± SD, 61 ± 18.8). Initial electrophysiological study revealed A-H intervals of 55 to 188 msec (mean 96 ± 27.2). H-V intervals ranged from 24 to 100 msec (mean 50 ± 13.8), with prolonged (>55 msec) H-V in 18 pts (21%). Pts were prospectively followed for 26 to 2210 days (mean 888 ± 563). A-V block developed in three pts (4%), on days 6, 974 and 1453 respectively. In all three, site of block was distal to H (two spontaneous and one secondary to hyperkalemia). Twenty-two pts died (26%), nine (10% of total) due to cardiovascular causes (six sudden).

In conclusion, PBFB was associated with a 21% incidence of trifasicular disease, and a small but definite risk of trifasicular A-V block. The relatively high cardiovascular mortality suggests that PBFB as defined above, is sometimes associated with clinically significant organic heart disease.

LIDOCAINE UNMASKS LATENT ATRIOVENTRICULAR BLOCK DUE TO ISCHEMIA

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Although the effect of lidocaine (L) on atrioventricular conduction (AVC) in normal conduction tissue is negligible, its effect after ischemic damage is not known. His bundle (H) recordings were taken before and 3 to 6 days after anterior septal artery (ASA) ligation in the dog at various heart rates both before and following the administration of L in a dose of 4 mg/kg. In dogs without ASA ligation, L had no significant effect on AVC; AV nodal block occurred in 4 out of 7 at pacing rates of 300 beats per minute before L and 4 out of 5 after L. In no instance did block distal to H or in the bundle branches occur. In another 11 dogs who underwent ASA ligation, L significantly increased the H-V interval during sinus rhythm and at all pacing rates up to those at which block appeared. L also increased the occurrence of AVC block. Three of the ischemic animals had AVC block before L, 2 AV nodal and 1 H block and 8 had AVC block after L ($p<.05$). H block occurred in 3, AV nodal block in 4, and right bundle branch block in 1. The H-V time during sinus rhythm in those dogs which developed H block after L, 49.9±4 (n=3), was longer than those which did not, 29.3±2 (n=8, $p<.001$) indicating that the ability of L to produce H block is directly related to the H-V time after ischemic damage. We conclude that L can unmask latent AV nodal, H, and bundle branch conduction system defects in the chronic ischemic state.

RIGHT VENTRICULAR CONDUCTION TIMES IN ASYMPTOMATIC ISOLATED RIGHT BUNDLE BRANCH BLOCK

Barry L. Alpert, MD; Robert N. Schnitzler, MD, FACC, and John H. Triebwasser, MD - USAF School of Aerospace Medicine, Brooks Air Force Base, Texas

Study of right ventricular conduction by endocardial mapping in right bundle branch block (RBBB) in a hospital population and in pacer-induced functional RBBB reveals impairment within the main right bundle branch (RM), as manifested by delayed right ventricular apex (RVA) activation. To elucidate the nature of the delay in asymptomatic isolated RBBB, mapping during electrophysiologic study for aeromedical disposition was performed in 10 aircrew members, average age 34 years (range 20-48). Four with RBBB without other evidence of heart disease were compared to six without RBBB with either a remote episode of atrial fibrillation (4), possible sinus arrest (1), or atrial ectopic rhythm (1). Filtered recordings from the His (H), RB, right ventricular inflow tract (RVIT), RVA, and right ventricular outflow tract (RVOT) were obtained with catheters with 1 cm interelectrode distance and were recorded with surface leads I and MCL1 at 200 mm/sec. Five separate sinus beats for each patient were analyzed with a computer-assisted sonic tablet and averaged. The results for mean and standard deviation for each group were:

	H-RB	H-Q	H-RVIT	H-RVA	H-RVOT
Normal	10±1	51±5	68± 7	69±10	90± 7
RBBB	11±1	51±4	72±10	78± 9	128±17
	NS	NS	NS	NS	p<0.01

Thus, RVA activation was normal with delayed RVOT depolarization, reflecting an intact main RB. This finding is similar to right ventriculotomy-induced RBBB and suggests that RBBB in a young asymptomatic population is due to distal block, making progressive conduction delay unlikely.

PERMANENT PROPHYLACTIC PACING IN PATIENTS WITH CHRONIC BUNDLE BRANCH BLOCK

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177 patients with chronic bundle branch block underwent His bundle recordings and were followed prospectively. 33 underwent prophylactic (no documented 2° or 3° atrioventricular block) pacemaker insertion at the discretion of the referring physician (group 2), whereas 144 did not (group 1). There was no significant difference in age (66 ±15 vs 69±8 yr), serum cholesterol (208±22 vs 206±45 mg/100 ml), or incidence of transient neurologic symptoms (75/144, 52%, vs 23/33, 70%), hypertension (44/144, 31%, vs 14/33, 42%), coronary artery disease (CAD) (103/144, 72%, vs 26/33, 79%), severe congestive heart failure (CHF) (41/144, 28%, vs 10/33, 30%), or mean follow-up time (21±16 vs 18±15 mo) between groups 1 and 2, respectively. Group 2 patients had a longer mean infranodal conduction time (HQ) (77±24 vs 61±20 msec, $P<0.01$) than group 1 patients. On follow-up, more group 2 patients had relief of neurologic symptoms than group 1 patients (14/17, 82%, vs 30/52, 58%) (3 in each group died before symptom relief could be assessed), but the difference was not statistically significant ($0.1<P>0.05$). There was no significant difference between groups 1 and 2 in total mortality (50/144, 35%, vs 16/33, 48%) or incidence of sudden death (15/144, 10%, vs 6/33, 18%). Only 6/50 (12%) of group 1 deaths and 1/16 (6%) of group 2 deaths had neither CHF nor CAD. 1)Prophylactic pacing in a group of largely symptomatic patients with chronic bundle branch block and prolonged HQ intervals appears to be effective in relieving transient neurologic symptoms but fails to alter overall mortality or prevent sudden death; 2)mortality was related to type and severity of underlying heart disease.

PROGNOSTIC SIGNIFICANCE OF LEFT ANTERIOR HEMIBLOCK WITH RIGHT BUNDLE BRANCH BLOCK IN MASS SCREENING.

H. E. Kulbertus, MD, FACC, F. de Leval-Rutten, MD, M. Dubois, MD and J. M. Petit, MD, Malvoz Institute and University of Liège. Liège. Belgium.

An EKG was taken in all subjects aged 35 or over attending a screening centre for cardiovascular and pulmonary diseases. 28,531 subjects (46.6% male ; 53.4% female) were examined. Intraventricular conduction defects (IVCD) were more common in men than in women and increased in frequency with advancing age. The relative incidence of each is indicated in the table. Between 1972 and 1976, 106 instances of LAHB-RBBB were discovered (78 male, 28 female, mean age: 68 yrs ± 7.8). Hypertension, angina, cardiomegaly, or frequent VPB's were noted in 52%, 23%, 16% and 12% of the cases, respectively. During a follow-up of 1 to 5 yrs (m: 34.7mths), 10 deaths were recorded (none sudden, 3 cardiac). Cumulative mortality at 2 and 4 yrs was 3.23 and 8.65%, respectively, which was not different from mortality in matched controls. Only 2 patients progressed to heart block. It is concluded that, in mass screening, LAHB-RBBB neither has ominous implications, nor justifies conduction studies even in elderly subjects with hypertension, or angina.

Table. IVCD. Mean incidence (per 1,000).

	male	female	
Isol. LAHB	87.4	59.2	$p < 0.0005$
LBBB	6.0	8.8	$p < 0.01$
Isol. RBBB	13.1	6.4	$p < 0.0005$
LAHB-RBBB	5.3	1.2	$p < 0.0005$
No BBB	888.2	924.5	$p < 0.0005$

EARLY AND LATE RECURRENT CARDIAC ARREST. PROGNOSTIC VALUE OF HEART BLOCK AND VENTRICULAR CONDUCTION DEFECTS

Alvaro Mayorga-Cortes,MD.FACC,Cesar A.Conde,MD.FACC. Robert J. Myerburg,MD.FACC. Division of Cardiology, The University of Miami School of Medicine.Miami,Florida

For the last 3 years 73 patients(pts)entered the hospital alive after cardiac arrest in the community. Fourteen pts have had 16 episodes of recurrent CA,early (within 4 weeks of the first arrest)in 9 pts and late (more than 4 weeks)in 7 pts,with only two survivors. Seven pts (50%) had heart block in the Coronary Care Unit(CCU) : first degree in 2 pts (14%) and complete heart block (CHB) in 5 (35%)and all seven pts died of recurrent CA (early in 5 pts and late in 2). Nine pts (64%) had conduction defects on admission. Left bundle branch block (LBBB) in 5 pts (35%),right bundle branch block (RBBB) in 2 pts (14%) and 2 pts (14%) with other intraventricular conduction defects (IVCD). Three out of the 5 pts with LBBB experienced CHB in the CCU and the 5 pts died of recurrent CA(early in 3 pts and late in 2). The 2 pts with RBBB died of early recurrent CA and none of them manifested CHB during the CCU period. Of the 2 pts with other IVCD,one pt had CHB in the CCU and died of recurrent CA. In summary, post CA pts with IVCD at the time of admission, are at a very high risk for early and late recurrent CA, and for the development of A-V block during the CCU period. Temporary and permanent pacemaker therapy deserves evaluation in this group of patients.

EFFECTS OF IMIPRAMINE HYDROCHLORIDE ON ELECTROPHYSIOLOGICAL PROPERTIES OF SHEEP CARDIAC PURKINJE FIBERS

Francis M. Weld, MD, FACC; J. Thomas Bigger, Jr., MD, FACC; Daniel Swistel; John Bordiuk, Columbia University, New York, New York

Imipramine (IMI) suppresses ventricular arrhythmias in dogs and in man, and IMI toxicity causes severe intraventricular conduction disturbances. To define the cellular electrophysiological causes of these actions, we investigated the effects of IMI at $3x10^{-8}$ to $3x10^{-6}$ g/ml on the action potential characteristics of Purkinje fibers (PF) driven at 60/minute, and on PF exhibiting spontaneous automaticity. The half-time to maximum depression of phase 0 depolarization ($\dot{V}_{max}$) was 30 minutes. Dose-response studies at one hour of IMI superfusion (75% of steady state depression) showed 50% depression of $\dot{V}_{max}$ by IMI at 10^{-6} g/ml. Most fibers became refractory to external stimulation (while fully polarized) after one hour of exposure to IMI at $3x10^{-6}$ g/ml. IMI shortened action potential duration at a concentration one-tenth of that reducing $\dot{V}_{max}$. IMI did not depress the slope or magnitude of spontaneous phase 4 depolarization at concentrations high enough to render PF refractory to external stimuli ($\geq 10^{-6}$ g/ml). Spontaneous firing due to isoproterenol and/or hypokalemia ceased in IMI at 10^{-6} g/ml, due to a positive voltage shift in threshold for excitation. Thus, IMI shares some electrophysiological actions with either lidocaine or quinidine, but does not depress phase 4 depolarization. We conclude that IMI's depression of the early inward transient current produces its antiautomatic effect and also the electrocardiographic QRS widening seen during IMI toxicity.

ELECTROPHYSIOLOGIC EFFECTS OF PROCAINAMIDE IN PATIENTS WITH NORMAL AND PROLONGED SINOATRIAL CONDUCTION TIMES.

D. George Wyse, MD, PhD; John H. McAnulty, MD, FACC; Michael Stadius, Shahbudin H. Rahimtoola, MD, FACC, University of Oregon Health Sciences Center, Portland, Ore.

Effects of procainamide (P) on sinus node (SN) and atrium were evaluated in 16 patients (pts); 5 had paroxysmal supraventricular tachycardia (SVT), 2 had syncope and bradycardia, and 9 had bundle branch block. P was given as a divided IV bolus (8mg/kg) and continuous infusion (0.05mg/kg/min) followed by an additional 4mg/kg bolus and an infusion of 0.075mg/kg/min. Plasma levels (mcg/ml, mean ± SE) at 0 and 15 min during recording were 7.3 ± 0.5 and 6.0 ± 0.4 and rose ($p<0.05$) to 11.8 ± 0.9 and 10.1 ± 0.7 after the second bolus.

Cycle length (CL) (msec, mean ± SE) after P decreased (848 ± 43 vs 799 ± 42, $p<0.01$). SN recovery time fell after the lower dose of P at CL 500 (1166 ± 81 vs 1024 ± 9, $p < .02$). At the higher dose of P it fell at CL 462 (1066 ± 134 vs 915 ± 129, $p<0.05$). Sinoatrial conduction time (SACT) could be calculated in 11 pts and fell significantly (105 ± 11 vs 90 ± 9, $p<0.05$) after P. SACT was not related to CL before ($r = 0.39$) or after P ($r = 0.38$). Atrial effective and functional refractory periods increased significantly with: a) larger dose; b) during atrial pacing; and c) in pts with normal SACT. In those with prolonged SACT (>115msec) the change was not significant.

Seven of 9 zones of sinus echo and 4 atrial echo zones producing SVT were abolished by P.

These effects of P on sinus node and atrium suggest it may be useful in SVT and other atrial dysrhythmias but the effects are less predictable in pts with increased SACT and high therapeutic doses may be needed in some pts.

THE HUMAN ANTERIOR MITRAL VALVE LEAFLET AS A POSSIBLE SITE OF ORIGIN OF ATRIAL ARRHYTHMIAS

John J. Fenoglio, MD; Keith Reemtsma, MD, FACC; Allan J. Hordof, MD; Andrew L. Wit, PhD, College of Physicians and Surgeons, New York, New York, 10032

Our previous studies have shown that cardiac muscle in the anterior mitral valve leaflet (MV) of dogs and monkeys can initiate automatic impulses and might act as a site of origin of atrial arrhythmias. Although cardiac muscle has been demonstrated in the human MV the electrophysiologic properties and ultrastructure of these muscle fibers have not been characterized. We studied the MV and adjacent left atrium from the heart of a recipient of a cardiac transplant. The MV was normal histologically. Transmembrane potentials were recorded during Tyrodes superfusion. Cardiac fibers in the midportion of the MV had maximum diastolic potentials of 68±9 mV and action potentials with slow upstrokes ($\dot{V}_{max}$<10 V/sec) and low amplitudes (71±4 mV). They showed phase 4 depolarization and initiated automatic impulses at a rate of 62/min. During electrical stimulation norepinephrine (1.0 µg/ml) caused the appearance of delayed afterdepolarizations(DA). When stimulus rate was increased DA amplitude increased until it reached threshold, triggering nondriven sustained rhythmic activity (rate=125/min). DA's and triggered activity were abolished by acetylcholine and verapamil. Subsequent ultrastructural study demonstrated atrial muscle with specific granules in the MV in direct continuity with the left atrial myocardium. In the midportion of MV the muscle fibers were 1-3µ in diameter, were arranged in longitudinal bands with intercalated discs at the cellular poles, lacked side-to-side junctions and bands of fibers were separated from one another by fibrous tissue. The mitral valve may therefore act as a site of ectopic impulse initiation in the human heart.

ELECTROPHYSIOLOGICAL EFFECTS OF IMIPRAMINE ON CARDIAC PURKINJE FIBERS

David Rawling, BA, and Harry A. Fozzard, MD, FACC, University of Chicago, Chicago, Illinois

Imipramine produces ECG changes in patients; further, many overdose victims die of cardiac arrhythmias. The drug has been implicated in sudden death, and has been considered a possible antiarrhythmic agent. Given these observations we wondered if these phenomena could be the result of a direct action of imipramine on cardiac tissue, or were secondary to its known parasympatholoytic and sympathomimetic effects. Using standard electrophysiological techniques, we examined the dose-response relationship of imipramine and the membrane excitability properties of cardiac Purkinje fibers using intracellular current injection. Imipramine at a conc. of 1000 ng/ml decreased $(dv/dt)_{max}$ by 46%, action potential duration by 44%, and conduction velocity by 27%. This reduction of action potential duration is unlike the effect seen with quinidine, to which imipramine has been compared. In addition, membrane responsiveness experiments showed a reduction in $(dV/dt)_{max}$ for all membrane voltages (V_m), a decrease in the lowest V_m at which the fiber could be stimulated, and a slowing of the time constant of recovery of the inward current. In conclusion, we have shown that imipramine has profound effects upon cardiac Purkinje fibers and that these effects are unlike those of quinidine. These findings account for many of the ECG changes seen in patients who have taken this drug, and help to understand its effect on excitability.

A CLINICALLY PRACTICAL DISPLAY FOR ELECTROCARDIOGRAPHIC SURFACE POTENTIAL MAPPING

Robert L. Lux, PhD; J.A. Abildskov, MD, FACC; A. Kerry Evans, ME; Mary Jo Burgess, MD; G. Michael Vincent, MD, FACC; University of Utah, Salt Lake City, Utah

Extensive ECG examination using body surface potential maps has been shown to improve recognition of myocardial infarction, hypertrophy, preexcitation sites and other important abnormalities. Increased medical use of mapping is dependent upon practical methods for processing and displaying the large quantities of data acquired. Toward this end, 12 mathematically independent (orthogonal) surface potential distributions (basis patterns) were extracted from about 20,000 map frames obtained from 192 simultaneously recorded ECGs on 221 subjects. Data for each map were displayed as 12 traces, each representing the component of each basis pattern throughout the cardiac cycle. All information contained in serial isopotential maps obtained from 192 leads is represented by the 12 tracings in that the maps may be reconstructed from them to a high degree of accuracy (30 μV rms). The tracings resemble familiar ECG leads and are appropriate for quantitating correlations of waveform and disease states. ECG features with established diagnostic utility were readily apparent in the new traces, including QRS abnormalities incident to myocardial infarction, conduction disorders and ST-T abnormalities. A unique feature of the basis patterns is their apparent relationship to the multipole series. The first 3 are "dipolar" and the remaining 9 are "nondipolar". Diagnostic value of this feature was illustrated in traces from patients with inferior wall infarction which had significantly greater nondipolar voltage than normals. The new traces provide a means of storage display and handling of surface potential maps in a form suitable for practical medical use.

TUESDAY, MARCH 7, 1978
PM
PEDIATRIC CARDIOLOGY—I
2:00 to 5:30

SPECTRUM OF CARDIOVASCULAR ANOMALIES FOLLOWING CARDIAC LOOP CONSTRICTION IN THE CHICK EMBRYO

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The interrelationship of blood flow and cardiovascular (CV) morphology has always intrigued cardiac embryologists. This study describes a spectrum of anomalies in chick embryos with conotruncal constriction during cardiac septation. Stage 21 embryos were prepared by removing a portion of the shell and membranes and incising the chorion. A 10-0 nylon suture was knotted around the cardiac loop, constricting the conotruncus to a diameter of 0.4mm. Shells were sealed with parafilm and eggs reincubated. In 39 embryos the loop was removed after 2, 6 or 24 hours and in 9 embryos left undisturbed until stage 36-43 (beyond completion of cardiac septation), when all embryos were either fixed with 10% formol or injected intravascularly with acrylic and studied after microdissection or tissue digestion. Aortic and pulmonary root, aortic arch (AA), brachiocephalic and pulmonary artery diameters were measured; 65 control embryos were similarly studied. The spectrum of CV anomalies included absent, interrupted or coarcted AA, ventricular septal defect (VSD) and persistence of left fourth AA, and incidence was directly related to loop duration. Seven (77%) embryos with undisturbed loops and 2 (8%) control embryos had CV anomalies. Aortic root diameter was smaller ($p<.05$) than pulmonary root in all embryos with interrupted or absent AA, and larger ($p<.01$) in embryos with persistent left AA. Embryos with VSD had normal aortic and pulmonary root diameters but increased AA and brachiocephalic artery diameters ($p<.001$). Since biorheology in embryonic systems has shown that blood flow correlates directly with vessel diameter, we conclude that CV anomalies in the loop constricted hearts resulted from alteration of AA flow prior to cardiac septation.

MYOCARDIAL CONTRACTILE PROTEINS IN NEWBORN LAMBS: MATURATIONAL CHANGES IN Ca++ AND K+-ACTIVATED MYOSIN ATPASE ACTIVITY OF LEFT AND RIGHT VENTRICLES

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We have previously demonstrated age-related alterations in both pump and muscle performances of the myocardium of the newborn lamb. These mechanical properties of newborn myocardium may reflect biochemical activity of the contractile proteins. To assess biochemical properties of newborn myocardium, we examined Ca++ and K+-activated myosin ATPase activity in left and right ventricles of 15 newborn lambs (1-84 days) and 4 adult sheep. Tissue was obtained from the lateral walls of left and right ventricles;myosin was isolated by previously developed purification techniques utilizing $(NH_4)\ SO_4$ fractionation of myosin. Concentration of pure myosin was determined by the Lowry method and both Ca++ and K+ activated ATPase activities were determined by phosphate assay as described by Fiske and SubbaRow:

Myosin ATPase Activities ($uMPi/mg\ min^{-1}$) at 4mM ATP								
Age(days)		1	7	14	28	42	56	84	Adult
Left	Ca++	0.70	0.71	0.74	0.76	0.94	0.97	0.70	0.72
	K+	1.48	1.45	1.53	1.47	1.79	1.88	2.05	2.05
Right	Ca++	0.88	0.70	0.75	0.81	0.72	0.68	-	0.84
	K+	1.30	0.80	0.86	1.29	1.28	1.34	-	1.60

The results demonstrated age-related changes in contractile enzyme activity which are unique for each ventricle. The left ventricle adapts to the increasing work-load placed on it by increasing its contractile enzyme activity. In contrast, the ATPase activity of the right ventricle reflects the limited workload placed upon it in the first weeks of life. Our findings demonstrate an important adaptation of left and right ventricular neonatal contractile proteins to extrauterine life.

MYOCARDIAL DYSFUNCTION IN STRESSED NEWBORNS: THALLIUM SCANS IMPLICATE ISCHEMIA.

John P. Finley, MD; Robert Howman-Giles, MB; David L. Gilday, MD; Richard D. Rowe, MD, The Hospital for Sick Children, Toronto, Canada.

Severe perinatal stress is recognized as a setting for myocardial dysfunction and congestive heart failure (CHF) in some infants. Indirect evidence for true myocardial damage are observations of atrioventricular valve regurgitation and ischemic ECG changes. Recent pathological findings and specific myocardial enzyme measurements also suggest that newborn myocardial dysfunction results from ischemia. We present additional direct evidence to support this view. Seven newborns had a clinical diagnosis of myocardial ischemia and dysfunction, with perinatal distress, CHF, and Q or ST-T abnormalities in all cases. Echo and hemodynamic assessment showed severe functional impairment in 2 cases. Thallium-201 (Tl201) myocardial images at age 2-14 days showed in all cases negligible myocardial and increased pulmonary uptake, suggesting widespread ischemia. Infants of similar age with myocarditis or CHF had normal myocardial and pulmonary uptake, while 3 infants with anomalous left coronary from the pulmonary artery showed a discrete anterolateral infarct. Rapid clinical improvement occurred within 3-7 days. 2-5 months later, 2 infants had a persistent ischemic ECG but repeat Tl201 images in 5 demonstrated almost normal uptake. This data suggests myocardial dysfunction in stressed newborns is associated with global myocardial ischemia which may or may not be transient. The timing and nature of the insult causing the ischemia are unclear.

LOCALIZATION OF CONDUCTION ABNORMALITIES IN VENTRICULAR INVERSION.

William L. Jackson, MD, Ulrich W. Busch, MD, Paul C. Gillette, MD,FACC Department of Pediatrics (Cardiology), Baylor College of Medicine and Texas Children's Hospital, Houston.

Ventricular inversion (VI) is frequently associated with conduction(C) disturbance, both congenital and acquired, but the nature and site of impaired C are controversial. Also,the feasibility of recording His bundle (H) potentials in the usual manner in these patients has been questioned.

We analyzed intracardiac electrograms obtained in 28 patients(pts) with VI. The H potential could be recorded via the right A-V valve in 21. Four of the 7 in whom the H could not be recorded had complete AV block (CAVB).Eight pts had documented CAVB prior to study. Completely normal intervals were found in 7 pts. Our study revealed the following:

	TOTAL # PTS	C TIMES (msec) RANGE	ULN	#PTS ABOVE ULN
HRA-LRA	14	12 - 56	40	4
A-H	19	60 -200	120	2
H-V	21	31 - 99	55	7

ULN= upper limit of normal, msec = milliseconds, HRA-LRA= high right atrium to low right atrium.

Of the 4 pts with CAVB in whom H potential could be recorded,the block was above the H in 3 pts, with H-V of 40, 57,73 msec respectively and below the H in one with A-H of 84 msec. Two pts with antegrade CAVB had capability for V-A conduction, manifested in one spontaneously during increased junctional rate,in the other, who had documented CAVB since birth, during V pacing.

Thus: (1) The H potential can be recorded in the usual manner in pts with VI, (2) one fourth of our pts had normal C intervals, (3) C disturbance in VI occurs at all levels, (4) CAVB in VI can be supra,infra and probably intra H.

NITROPRUSSIDE THERAPY IN CHILDREN WITH REFRACTORY CONGESTIVE HEART FAILURE.

Terrence Dillon, MD; George Benzing III, MD, FACC; Samuel Kaplan, MD, FACC. University of Cincinnati, Cinti, Ohio

Since nitroprusside (NP) can significantly increase cardiac output (CO) in patients with severely impaired left ventricular (LV) function, we infused NP in four children with intractable congestive heart failure (CHF) unresponsive to traditional therapy. Their ages ranged from 4-15 years. Two children had catheterization proven congestive cardiomyopathy with progressive deterioration over a two year period. The other two children had previously undergone open heart surgery (Septation of a single ventricle and a Rastelli procedure for complex TGV) one and three months earlier respectively. All patients exhibited severe CHF, low CO, and markedly dilated LV with poor contractility. NP was infused in a dose varying from 2.5-6.0 µg/Kg/min for periods ranging from 2-9 days. Thiocyonate levels were monitored in all. The patients with long standing congestive cardiomyopathy showed no response to NP. In both cases, inotropic agents were added, but both patients expired. In contrast, the post Rastelli patient showed a tenfold increase in urinary output (0.25-2.5 cc/Kg/hr) with marked symptomatic improvement on NP. She was subsequently discharged and ten months later has returned to a near normal level of activity. The second post surgical patient was treated with NP for a 48 hr period during which his urine output doubled (1-2 cc/Kg/hr). After NP was stopped he was again responsive to usual anti failure therapy and diuresed an additional 4.5 Kg over the next five days. Our experience with NP suggests that this agent may be useful in children with severe LV dysfunction and CHF who are unresponsive to traditional therapy. Further, the salutory effects of NP in these critically ill patients might be sustained on a long term basis with the use of long acting oral vasodilators.

DUAL ATRIOVENTRICULAR NODE PATHWAYS IN CHILDREN WITH AND WITHOUT DYSRHYTHMIAS.

Paul C. Gillette,MD,FACC and Mohinder K. Thapar, MD, Department of Pediatrics, Section of Cardiology, Baylor College of Medicine and Texas Children's Hospital, Houston.

Longitudinal dissociation of atrioventricular node (AVN) pathways have been demonstrated in experimental animals and in adult patients but have not been documented in children. Electrophysiologic records on 30 patients (8 months to 26 years of age) with paroxysmal supraventricular tachycardia (PSVT) or conduction abnormalities were analyzed. Dual AVN pathways were identified by finding discontinuous curves of AVN conduction intervals. While recording the His bundle electrogram, atrial extrastimuli were given at decreasing coupling intervals during either sinus or atrial paced rhythm. Demonstration of two different AVN conduction times and refractory periods or AVN echoes suggested dual AVN pathways. This phenomena was demonstrated in 13 of the 30 studies. Five of the 13 had no symptoms pertaining to arrhythmia: 2 of these had postoperative bundle branch block. One had small ventricular septal defect with 1° atrioventricular block, one, aortic stenosis, and one, PSVT. Of 8 symptomatic children, 6 presented with PSVT and 2 with transient atrioventricular block due to viral myocarditis. Of the 7 cases with PSVT, 6 were due to reentry within AVN and 1 to a concealed bundle of Kent. In this study we have documented the presence of dual AVN pathways in 43% of children studied for PSVT or conduction abnormalities.

Although only 8 of the 13 (46%) patients with dual AVN pathways had symptomatic dysrhythmias, the others may be at increased risk for developing dysrhythmias and require close follow-up.

PATENT DUCTUS ARTERIOSUS (PDA) AND INDOMETHACIN (INDO)--EXPERIENCE AND FOLLOW-UP

T.A. Merritt, MD; T.G. DiSessa, MD; S.E. Kirkpatrick, MD, FACC; L. Gluck, MD; W.F. Friedman, MD, FACC; University of California, San Diego, California.

Controversy exists about optimal management of PDA in the symptomatic preterm infant. Since 11/76, 43 pre-term infants required PDA closure for ventilator dependency, intractable heart failure and/or apnea-bradycardia. 29 infants (av. wt. 1190 gms, 7.5 days) received INDO (0.2 mg/kg, #18 p.o., #11 I.V.). Contraindications to INDO administration, (hyperbilirubinemia, renal dysfunction, bleeding disorder) resulted in PDA ligation in 17 (av. wt. 1253 gm, 9.5 days). 12 infants received 1 dose INDO, and 17 required multiple doses for sustained PDA closure. 4 INDO infants (14%) with severe RDS underwent subsequent PDA ligation; there was one fatality 2 days after surgery and in one infant the ductus was already constricted. Non-PDA related deaths occurred in 4 INDO (14%) and 2 ligated (12%) babies. Although INDO caused no significant increases in BUN or creatinine, urine formation was diminished for 24 hrs. after the drug ($p < 0.05$). When compared to ligated babies INDO treatment resulted in less assisted ventilation time ($p < .01$) and significantly less exposure to F_iO_2 greater than 0.3 ($p < .002$). A higher incidence occurred in ligated babies of post-intervention pulmonary problems but short term morbidity was otherwise comparable between the 2 groups. Long-term followup (up to 15 months) shows no difference between INDO and ligated infants in growth, neurological development, blood pressure, renal and visual function. The results of this study indicate that when used properly, inhibition of prostaglandin synthesis with INDO may substitute effectively for PDA ligation.

EXERCISE RESPONSES IN CHILDREN WITH PROGRESSIVE AORTIC REGURGITATION

Frederick W. James, MD, FACC; Richard Donner, MD, and Samuel Kaplan, MD, FACC, Univ. of Cincinnati, Cinti, Ohio

We assessed changes in blood pressure (BP), electrocardiogram (E-ECG) and working capacity (WC) during a strenuous upright bicycle exercise test (BET) in 30 patients (Pts) (Gr I) ages 6 to 23 years with dominant aortic regurgitation (AR). 114 normal children, ages 5 to 21 years were the matched controls (C). 20/30 Pts (60%) had left ventricular (LV) hypertrophy and/or cardiomegaly on chest radiograph. In 17/30 Pts, LV end diastolic volume (LVEDV) by echogram was used to provide additional subgroupings, Gr II (9) < 160% (average 73 ml/M^2) and Gr III (8) > 160% (average 118 ml/M^2) of predicted normal. Mean ± standard error LVED pressures were 7 ± 2 mm Hg in Gr II and 13 ± 1 in Gr III. The criterion for a positive E-ECG was ST depression (STD) ≥ 1 mm. BET was stopped if systolic pressure (SP) was ≥ 230 mm Hg and STD ≥ 3 mm. Mean ± standard error resting and exercise blood pressures are as follows:

C	Rest	PTS	C	Exercise	PTS
116±1/74±1	I)	126±4*/64±2+	167±3/83±1	I)	188±8*/74±3+
114±2/71±1	II)	116±3/64±3**	158±5/82±1	II)	164±8/71±6
120±2/76±1	III)	144±8+/65±7	178±4/84±1	III)	220±16**/75±4*

p < .05*, < .025**, < .01+

SP was > 230 mm Hg in 6 Pts of which 3 were in Gr III. 13/30 (43%) Pts developed STD (1 to 4 mm) on E-ECG with 2/13 in Gr II and 5 in Gr III as compared to 11/114 C (10%). Mean %shortening fractions by E, heart rates and WC in the subgroups were comparable to C. These data indicate that abnormal elevation of SP and STD on E-ECG occur with greater magnitude in Pts with larger LVEDV. We conclude that these results are important clues in the clinical management of children with AR.

ASSESSMENT OF RIGHT AND LEFT VENTRICULAR FUNCTION IN ASYMPTOMATIC PATIENTS AFTER MUSTARD'S OPERATION

Donald J. Hagler, MD, FACC; Donald G. Ritter, MD, FACC; Douglas D. Mair, MD, FACC; George D. Davis, MD; Erik L. Ritman, MD, PhD, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Postoperative assessment of right (RV) and left (LV) ventricular function was obtained at cardiac catheterization in 32 asymptomatic patients studied ½ to 11 years (mean 4.8) after Mustard operation for complete transposition of great arteries. The ages at operation ranged from ½ to 16 years (mean 4.5). RV function was assessed by 2 independent techniques of videodensitometric determination of ejection fraction and ventricular volume data. RV and LV volume determinations were obtained by computerized videoanalysis utilizing Simpson's rule. The mean RV ejection fraction by videodensitometry was 41% in 12 patients who had had intact ventricular septum (IVS); 39% in 4 patients with IVS and pulmonary stenosis (PS); and 38% in 6 patients with ventricular septal defect (VSD) and PS. By ventricular volume determination, the mean RV ejection fraction was 49% in IVS; 41% in IVS and PS; 34% in VSD; and 40% in VSD and PS. LV ejection fraction was significantly better: 62% in IVS; 54% in IVS with PS; 50% in VSD; and 63% in VSD and PS. This large series of long-term postoperative Mustard patients confirms our previous suspicions of decreased RV function with relatively preserved LV function. These observations support efforts for surgical correction utilizing the left ventricle as the systemic ventricle.

QUANTITATIVE RADIONUCLIDE ANGIOCARDIOGRAPHY-A RELIABLE METHOD FOR EVALUATING LEFT-TO-RIGHT SHUNTS IN CHILDREN

Robert A. Boxer, MD; Carl N. Steeg, MD, FACC; Peter Esser, PhD, Rashid Fawwaz, MD, and Philip Johnson, MD, Columbia-Presbyterian Medical Center, New York, N. Y.

To determine the accuracy and potential interobserver variability of quantitative radionuclide angiocardiography (QRA) in detecting and quantifying left-to-right (L→R) shunts, QRA was performed on 23 patients (pts), age 5 mos-16 yrs, m=6.8 yrs, within 2 hours of cardiac catheterization (CC). During CC, L→R shunts were verified by oximetry (Ox), and angiocardiograms. 18/23 pts had L→R shunts at either the atrial and/or ventricular or ductal levels. Each pt had QRA using technetium-99m pertechnetate (200μCi/kg) injected into the superior vena cava (n=10), external jugular vein (n=6), or antecubital vein (n=3). 4 pts had both superior vena caval and antecubital vein injections. Data were acquired at a rate of 2 frames/second with an Anger-type camera interfaced to a computer using a parallel-hole collimator. Shunt ratios (Qp/Qs) were determined by analyzing pulmonary transit curves using a gamma variate model. Qp/Qs values, calculated independently by 3 observers unaware of the clinical diagnosis, were matched to each other and to the CC Qp/Qs with excellent correlation (r=0.93). There was no significant interobserver difference. Qp/Qs ratios within a range of 1.2-3.0 could be accurately determined by the QRA method. Discrepancy in data in 2 pts with atrial septal defect may reflect the inadequacy of Ox. Every pt with a Qp/Qs ≥1.2/1 by Ox had a detectable L→R shunt by QRA. There were no false positive QRA shunts.

QRA is a simple and accurate technique for detecting and quantifying L→R shunts. Observer variability was not a factor. QRA serves as a screening procedure for L→R shunts, and may, with other appropriate evaluation, obviate the need for CC in selected pts.

LONG-TERM FOLLOW-UP OF PATIENTS WITH COMMON (SINGLE) VENTRICLE AFTER PALLIATIVE SURGERY

Douglas S. Moodie, MD; Abdul J. Tajik, MD, FACC; Donald G. Ritter, MD, FACC; W. Michael O'Fallon, PhD; Mayo Clinic and Mayo Foundation, Rochester, Minn.

Previously, we have described the natural history of common ventricle based on observation in 83 patients. Very little information is available regarding the course of patients with common ventricle after palliative surgery. We therefore obtained follow-up information on 84 of 95 patients with common ventricle who had undergone palliative surgical procedures. Diagnosis was established by selective large-film biplane angiography. At initial diagnosis, the patients (49 males, 35 females) ranged in age from 6 days to 25 years, with a mean age of 10 years. The mean follow-up period was 5 years (range 1 month to 25 years). Of the 84 patients, 33 died and 51 are alive. The survivors ranged in age from 1½ to 41 years (mean 15 years). According to NYHA classification, 26 of the survivors are in functional Class I or II, 21 in Class III, and 4 in Class IV. Systemic pulmonary artery shunts alone were performed in 43 patients, pulmonary artery banding in 15, and a combination of procedures in 26. Ten years after diagnosis, 70% of patients with type A common ventricle (outflow chamber present) who had undergone a palliative procedure are alive. In contrast, only 25% of patients with type C common ventricle (no outflow chamber) are alive. Because of the high attrition rate in these patients despite palliation, further attempts to perfect corrective surgery appear justified.

HEMODYNAMIC EFFECTS OF THE LEFT VENTRICLE-APICO-AORTIC CONDUIT TO RELIEVE LEFT VENTRICULAR OUTFLOW OBSTRUCTION.

Michael R. Nihill,MD, FACC, John C. Norman, MD, FACC, Dan G. McNamara, MD, FACC, Denton A. Cooley, MD, FACC. Department of Pediatrics(Cardiology)Baylor College of Medicine & Texas Children's Hospital and the Surgical Division of the Texas Heart Institute. Houston.

A valved Dacron conduit was placed from the apex of the left ventricle (LV) to the supraceliac abdominal aorta(Ao) in 19 patients (pts) with LV outflow tract obstruction untreatable by customary techniques. Postoperative results were assessed in 13 of 17 surviors 10 days to 6 months postoperatively by pressure measurements, LV and Ao angiography, and measurements of aortic blood flow velocity using a catheter-tip velocity probe.

Preoperative LV-Ao pressure gradients ranged from 60 to 140 mmHg (mean = 106) and fell to 5 - 60 mm Hg (mean 25) postoperatively. Ventriculography showed normal end-diastolic volume (mean 68.6 ± 1.5 ml/m^2) and cardiac index (mean = 4.43 ± 1.46 L/min/m^2).Ejection fraction was normal in all but one pt (45%), mean = 70.8 ± 11.8%. Systolic cavity obliteration,present in 7 pts preoperatively, disappeared in 3 pts and decreased in 4 pts, 3 of whom had a rigid LV outflow connector. Ventriculography was unreliable in assessing the portion of blood flow in each outlet of the LV since this varied with proximity of the catheter tip to either outlet. Blood flow direction and velocity were recorded with a catheter-tip velocity probe in the conduit (6 pts), ascending Ao(10 pts) and along the descending Ao (13 pts). These measurements, together with selective aortography, showed that the conduit carried 15.7 to 45% (mean = 34.5%) of the LV output. Retrograde flow to the aortic arch was seen in 7 pts.

Creation of a double outlet LV improved otherwise surgically untreatable LV outflow tract obstruction resulting in improved postoperative hemodynamics and LV function.

TUESDAY, MARCH 7, 1978
PM
CARDIAC ULTRASOUND
2:00 to 5:30

INTER-OBSERVER VARIABILITY IN THE QUANTITATIVE EVALUATION OF M-MODE ECHOCARDIOGRAMS: SURVEY AND RECOMMENDATIONS

David J. Sahn, MD, FACC; Anthony DeMaria, MD, FACC; Joseph Kisslo, MD, FACC; Arthur Weyman, MD, FACC; The Committee on M-Mode Standardization of the American Society of Echocardiography; Tucson, Az., Davis, Ca., Durham, N.C. and Indianapolis, In.

In order to evaluate measurement criteria and measurement reproducibility in M-mode echo, 400 measurement surveys, each consisting of 5 echoes, were distributed; 76 (380 echoes-19%) were measured and returned. For each structure and measurement criterion, the mean of the measurement, the 95% confidence limit (1.97 standard deviations) and mean percent uncertainty (MPU)(95th percentile confidence limit divided by the mean X 100) were calculated. Left ventricular (LV) minor axis diameter in diastole appeared more reproducibly measured at the onset of the QRS (MPU=8.2%) than at the peak of the QRS (MPU=11.8%). Systolic LV dimension showed a MPU of 15.2% at the peak of posterior wall motion and 15.0% at the nadir of septal motion. Septum (MPU=19.5%) and LV posterior wall thickness (MPU=23.4%) showed surprising variability on end diastolic measurements. Aortic root outer-inner (leading edge) dimension in systole (MPU=13.8%) and left atrial dimension (systole)(MPU=11.2%) were quite reproducible, but right ventricular cavity dimension (MPU=28.8%) at the onset of the QRS (34.8% at the peak of the QRS) and right ventricular anterior wall thickness (MPU=72.4%) showed high measurement scatter. Examining the surveys themselves allowed common reading errors to be identified. The study provides for a more reasonable use of echocardiographic quantitation by establishing the levels of inter-observer variability and stresses the need for strict standardization of technique and measurement. The report will recommend new criteria for measurement of M-mode echocardiograms.

AN ANALYSIS OF THE REPRODUCIBILITY OF 2-DIMENSIONAL ECHOCARDIOGRAPHIC MEASUREMENTS

Ming K. Heng, MD, H.L. Wyatt, PhD, Samuel Meerbaum, PhD, FACC, Julius Woythaler, John Hestenes, PhD, Robert Davidson, MD, FACC, Eliot Corday, MD,FACC, Cedars-Sinai Medical Center, Los Angeles, Calif.

The reproducibility (R) of 2-dimensional echocardiographic measurements in clinical and dog studies was determined using an 84° phased array sector scan (PASS). Since the left ventricular (LV) cross-sectional area was basic to all our computations of LV function with the PASS, duplicate measurements of this parameter at mid-LV level was used to evaluate R,which was calculated by the percentage deviation from the mean of duplicate measurements, i.e. $(\frac{X-x}{X})$ 100, where X = mean of duplicate measurements, x = value for one of the 2 measurements. The R for epicardial (EPI) and endocardial (ENDO) frames in end-diastole and end-systole was determined for (a) one observer's assessment of a single frame twice (Intraobserver), (b) 2 observers independent assessment of a single frame (Interobserver), (c) one observer's assessment of 2 consecutive cardiac complexes (Beat-To-Beat). In all instances there was no significant difference between duplicate measurements. The percentage deviations (average ± SD) are:

PATIENTS (n=10)	END-DIASTOLE		END-SYSTOLE	
	ENDO	EPI	ENDO	EPI
INTRA-	3.7±4	3.2±2.6	6.0±3.7	5.2±4.5
INTER-	4.8±4.5	6.5±5.6	7.5±7.5	4.9±3.6
BEAT-TO-BEAT	5.0±2.5	3.3±2.9	6.1±6	3.8±1.8
DOGS (n=10)				
INTRA-	6.1±5.8	5.0±3.4	5.2±6.3	3.7±4.8
INTER-	5.1±3.8	4.6±4.5	4.1±4.2	1.2±1
BEAT-TO-BEAT	5.1±1.5	4.8±1	6.8±1.7	1.8±0.9

Conclusion: These results show that the variations in duplicate PASS measurements of LV cross-sectional areas are small. Thus, 2-dimensional echocardiography can be useful for the quantification of LV function.

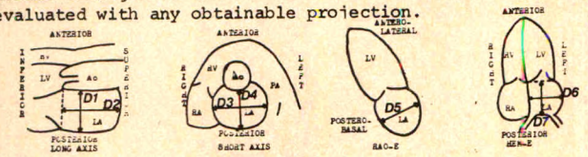
COMPARISON OF FOUR TWO-DIMENSIONAL ECHOCARDIOGRAPHIC VIEWS FOR MEASURING LEFT ATRIAL SIZE

S.E Schabelman, MD; N.B. Schiller, MD, FACC: R.A. Anschuetz, MD; N.H. Silverman, MD, FACC; S.A. Glantz,PhD, University of California, San Francisco, Ca.

The left atria of 60 patients were examined by M-mode and by wide angle two-dimensional echographic techniques to establish normal values for 7 end-systolic axes obtained from 4 tomographic projections and to compare these measurements with M-mode (DM). Nineteen patients were normal (NL), 21 had cardiomyopathy (CM), and 20 had mitral valve disease (MVD) diagnosed clinically, echocardiographically and, in 14, hemodynamically. The projections were the long and short axes, via precordial window and the right anterior oblique and hemiaxial equivalents (RAO-E & HEM-E) from the apex. The left atrial diameters are shown below. The measurements in mm were:

	D1	D2	D3	D4	D5	D6	D7	DM
NL(mean±SD)	25±4	34±4	36±4	26±4	33±5	33±6	35±6	27±4
CM	32±8	43±9	41±6	34±5	40±9	39±7	43±8	38±5
MVD	39±9	50±9	55±9	43±9	45±8	49±8	53±9	50±9

All dimensions correlated significantly with each other; in particular, the correlations with M-mode were between .82 and .86($p<.001$). We conclude that linear measurements of left atrial size from four projections were closely correlated with M-mode through a range of atrial size and with each other. These findings suggest that the left atrium enlarges in all axes and that it can be adequately evaluated with any obtainable projection.



BIPLANE MEASUREMENTS OF LEFT AND RIGHT VENTRICULAR VOLUMES USING WIDE ANGLE CROSS-SECTIONAL ECHOCARDIOGRAPHY.

Khalid R. Chaudry, MD, Satoshi Ogawa, MD, Ferrel J. Pauletto, MD, FACC, Francis E. Hubbard, MD, Leonard S. Dreifus, MD, FACC, Lankenau Hospital, Philadelphia, Pa.

Forty-seven patients (pts) undergoing left ventricular (LV) single-plane cineangiography were studied with a phased array 84° sector scanner. LV and right ventricular (RV) volumes (V) were measured from biplane images of cross-sectional echocardiography (Echo). (1) A major LV axis (L) was obtained with an apex Echo view (an image equivalent to an angiographic right anterior oblique view) and two minor axes (antero-posterior, D_1, and lateral D_2) were obtained on a short axis view of LV at the level of the mitral valve tip. The LV-V was calculated at end-diastole (EDV) and end-systole (ESV) by: $V=4/3\pi(L/2)(D_1/2)(D_2/2)$. (2) The RV-V was given by the formula for a pyramid with a triangular base: V=A x H/3, where A=an area of a triangular base; H=height of a pyramid. "A" was determined by planimetry on a hemiaxial view obtained by an apex Echo. "H" was measured on a sagittal cross-section view of RV. Results: Technically satisfactory images for LV and RV measurements were obtained in 30 pts including 20 pts with coronary artery disease. Echo-EDV, ESV, stroke volume (SV) and ejection fraction (EF) of LV were correlated significantly with angiographic (Angio) data (r=0.86, 0.91, 0.74 and 0.73) in pts with normal-sized LV as well as large spherical LV. Correlation was shown between Echo RV-SV and Angio LV-SV only when Angio LV-EDV was less than 170 ml (r=0.86 N=9). Echo RV-SV underestimated Angio LV-SV by 16-86 ml. The mean values for RV-SV and RV-EF were 41.6±12.7 ml (±SD) and 55.4±11.2%. It is concluded that 1) Echo provided a reliable technique for the biplane determination of LV-V, especially in pts with dilated hearts, and 2) RV measurements were of limited value in evaluating RV performance.

M MODE ECHOCARDIOGRAM OF THE CORONARY ARTERY

Kiyoshi Inoue MD; Keiichi Kuwaki MD; Keiko Ueda MD; Tetsuro Shirai MD; Toshinori Utsunomiya MS, Cardiovascular Center, Tokyo Metropolitan Police Hospital, Tokyo, Japan.

The clinical applicability of a new method for recording M mode display of the origin of left main coronary artery (LMCA), developed in our laboratory, was evaluated with verifing its identity by visualizing catheter and contrast media and with observing changes in the diameter of LMCA follwoing sublingual nitroglycerin (NTG) administration in 21 patients having coronary artery disease undergoing coronary angiography. Using Toshiba model SSL-53H real time cross sectional linear scanner and placing the probe of 85 mm in length along cardiac long axis, simultaneous cross sectional picture of out flow tracts of two ventricles, pulmonic valve (PV), aortic valve (AV) and sinus of valsalva (SV) was obtained. By turning the probe toward short axial direction holding SV as the center of the probe, LMCA was observed for the length from 5 to 20 mm. The M mode of LMCA was obtained by selecting beam on the line of LMCA. The two walls of LMCA were seen as two parallel echoes in the M mode display and the picture was much clearer than cross sectional. The catheter inserted and the dye injected into LMCA was visualized. NTG administration changed the diameter of LMCA for 1.5 to 3 times as wide of control. Using standared echocardiography and probe, the recordings of M mode display were repeatedat the bed side in all patients. By appling standared probe at 2nd left interspace, projecting it to the PV direction, and shifting slightly to AV, clear parallel echoes of two walls of LMCA were obtained in all cases. NTG administration changed the diameter of LMCA from 1.1 to 3.8 time as wide. M mode display of the LMCA are easy to record and the picture are clearer than those of cross sectional.

CLINICAL UTILITY OF IDENTIFICATION OF THE RIGHT VENTRICULAR OUTFLOW TRACT, PULMONARY ARTERY AND ITS BIFURCATION BY CONTRAST TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Martin Klicpera, MD; Theodore D. Fraker, Jr., MD; Joseph Kisslo, MD; Duke University Medical Center, Durham, NC.

Two-dimensional echocardiographic (2DE) examinations of the right ventricular outflow tract (RVOT), pulmonary artery (PA) and its bifurcation (BIF) were obtained using a focused phased-array imaging system in 75 consecutive adult patients (PTS) in order to assess the utility of this approach for the identification of potential cardiac disorders involving these structures. The ultrasonic technique was combined with several rapid injections of 10 ml. of normal saline into an antecubital vein to introduce microcavitations into the right-sided cardiac chambers and vessels. Adequate images of the RVOT, PA and BIF along with microcavitations were seen in 58 PTS (77%).

Pulmonary insufficiency was detected in 2 PTS, compression of the right main stem PA due to tumor was found in 1 PT, dilatation of the PA due to large left to right shunt was found in 4 PTS, negative contrast entering the PA due to a high ventricular septal defect was found in 1 PT. In addition, an abscess involving the area between the right coronary sinus of valsalva and the proximal pulmonary artery due to bacterial endocarditis could be identified.

These data indicate that: (1) adequate images of the RVOT, PA and BIF could be obtained using contrast 2DE, (2) useful clinical information concerning several types of cardiac disorders involving these structures can be obtained using this method and (3) further studies are indicated to investigate the specific applicability of this approach for evaluation of intrinsic or extrinsic abnormalities of the RVOT, PA and its branches.

THE ASSESSMENT OF THE RIGHT ATRIUM USING APEX-SECTOR ECHOCARDIOGRAPHY

Fredrick G. Kushner, MD; Wilfred Lam, MD; Patricia Klunder, BS; Joel Morganroth, MD, FACC, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Using an apex view with the cross sectional SKF Echo-sector (ASE), right atrial (RA) and left atrial (LA) dimensions were evaluated in 25 patients (pts)(13 males, age 17-76 yrs) and compared to the LA, left ventricular (LV) and right ventricular (RV) dimensions as measured using the M-mode echocardiogram. Data were obtained in the following groups: secundum (2°) and primum (1°) atrial septal defects (ASD), congestive cardiomyopathy (CCM), idiopathic hypertrophic subaortic stenosis (IHSS), valvular aortic stenosis (AS) and normals (NL):

	ASE (range in mm)		M-Mode (in mm)		
	RA	LA	LA	LV	RV
NL	30-39	30-39	23-36	40-49	14-26
AS	31-47	33-50	26-58	40-45	17-18
IHSS	40-50	32-50	32-40	40-45	14-19
CCM	48-60	40-55	30-49	54-73	13-19
1° ASD	50-60	40-60	34-53	31-51	11-34
2° ASD	50-60	32-40	29-32	35-42	24-45

Although the M-mode RV dimensions were normal in all pts with IHSS and CCM, the ASE-RA dimensions were abnormal in all cases. Similarly, in pts with RV volume overload (ASDs) the M-mode RV size may be normal in some cases, whereas the ASE-RA size was abnormal in all cases. There was a poor correlation between ASE and M-mode LA size. In conclusion, ASE is a valuable tool to evaluate RA dimension, and appears to be more sensitive than the M-mode echocardiogram in detecting right heart disease. In addition, ASE may provide a more complete evaluation of LA abnormalities.

USEFULNESS OF THE TIME INTERVAL HISTOGRAM (TIH) OF THE RANGE-GATED PULSED DOPPLER (RGPD) FOR DETECTING LEFT-TO-RIGHT ATRIAL SHUNTS (LRAS)

Stanley J. Goldberg, MD, FACC; Jose C. Areias, MD; Folkert de Villeneuve, MD; Silia Spitaels, MD; U. of Az., Tucson, and Erasmus U., Rotterdam.

The purpose of this investigation was to determine if children with LRAS could be separated noninvasively from those with other cardiac lesions exclusively by examination of the TIH of the RGPD. The RGPD allows Doppler sampling within a 2X4mm sample volume defined in location by the M-mode echocardiogram. TIH is a graphic frequency-time histogram created at a sampling rate of 4,000/sec., on which a frequency dispersion indicates nonlaminar flow. TIH dispersion in 96 instances of normal flow was less than 1 cm amplitude and thus, 1 cm was used as the upper normal limit. The study population consisted of 15 experimental children with LRAS and 43 acyanotic controls. The criterion for recognition of LRAS was diastolic TIH dispersion >1 cm amplitude with the range gate in the right atrial outflow tract. Observer bias was diminished because they 1) were unfamiliar with the children, 2) were blind to their diagnoses, 3) were protected from casual remarks by language barrier, 4) reported results by analyzing pooled, unmarked records independently by reference only to a code number. Under these circumstances, one examiner detected all instances of LRAS and the other detected 14/15 instances ($p<.01$). No false positives occurred for controls. An important difference between this and prior RGPD studies is that the present one evaluated only graphic TIH output whereas others relied principally on audible output for all judgements. TIH technique is more objective than the audible one and results can be evaluated by others without special audio equipment. This investigation demonstrates the clinical utility of graphic TIH output of the RGPD.

IDENTIFICATION OF LEFT VENTRICULAR THROMBI BY CROSS-SECTIONAL ECHOCARDIOGRAPHY

Alexander Neumann; William Bommer, MD; Lynn Weinert; Todd Grehl, MD, FACC; Dean T. Mason, MD, FACC; Ezra A. Amsterdam, MD, FACC; Anthony N. DeMaria, MD, FACC; University of California, Davis, California.

The detection of left ventricular thrombi (LVT) following myocardial infarction remains a difficult problem. Thus, we studied 15 consecutive infarction patients (pts) by M-mode and two-dimensional (2-D) echocardiography to assess the value of these techniques in the recognition of LVT. All pts had anterior infarctions and large antero-apical dyskinetic segments on cineangiography (cine). Three pts exhibited evidence of LVT consisting of recurrent systemic emboli (EMB). Two EMB pts showed apical filling defects on cine. The third EMB pt had a levophase cine which failed to demonstrate a defect, but was found to have a 2-3 cm apical LVT at surgery. No non-EMB pt had cine evidence of LVT. 2-D echo images were obtained along the long (LA) and short axes (SA) of the left ventricle with the transducer at the left sternal border; and in a hemiaxial (HA) projection with the transducer at the cardiac apex. Although the LA and SA views confirmed the presence of dyskinesis, they did not provide sufficient imaging of the apex to delineate an abnormal mass. However, in all 3 EMB pts intense echoes from a distinct apical mass were visualized with the HA view. No evidence of LVT was observed on 2-D exam in any of the non-EMB pts. M-mode echoes revealed apical akinesis in all pts, however despite multiple M-mode scans, no consistent echo producing mass could be visualized. Thus, although M-mode visualization of thrombi is unreliable in most pts, 2-D in the hemiaxial view provides clear demonstration of these masses and may obviate the need for angiography.

DIAGNOSIS OF VENTRICULAR SEPTAL DEFECT BY PULSED DOPPLER ECHOCARDIOGRAPHY - SENSITIVITY, SPECIFICITY, LIMITATIONS

J.G. Stevenson, MD.; I. Kawabori, MD.; T.K. Dooley, BS.; and W.G. Guntheroth, MD.; University of Washington Hospital, Seattle

The M-mode echocardiographic findings of ventricular septal defect (VSD) are usually non-specific. A VSD is suspected when turbulent blood flow is detected in the right ventricle by pulsed Doppler echocardiography (PDE), and a specific PDE diagnosis of VSD can be made by following the turbulent VSD jet through the septum. In order to assess the sensitivity, specificity and limitations of PDE diagnosis of VSD, 105 children undergoing cardiac catheterization were examined by PDE. Catheterization diagnoses included VSD in 51 (isolated in 31, with transposition of the great arteries (TGA) in 3, tetralogy 7, A-V canal 5, truncus arteriosus 5). The PDE diagnosis of VSD was made in 46/51 = 90%. There was one false positive diagnosis of VSD in a youngster with left ventricle to right atrial shunt but no clear VSD, yielding a specificity of 98%. Five had VSD jets which could not be followed through the septum: 1 in unusual (apical) location, 1 in TGA with shunt from anatomic RV to LV (unusual flow direction) 3 in youngsters with large VSD and elevations of pulmonary resistance ranging from 8.9 to 13.3 units (little VSD turbulence, no discrete jet to follow). The presence of additional shunts (atrial, ductal) did not compromise our ability to diagnose VSD by PDE. The PDE detection of isolated, or complicated VSD with overall sensitivity of 90% and specificity of 98% has obvious clinical utility. The PDE diagnosis of VSD may be more difficult however in cases with unusual VSD location or flow direction, or with elevated pulmonary resistance.

ECHOCARDIOGRAPHIC DIFFERENTIATION OF PARTIAL AND COMPLETE ATRIOVENTRICULAR CANAL

John L. Bass, M.D.; F. Blanton Bessinger, Jr., M.D.; Cheryl Lawrence; University of Minnesota; Minneapolis, Minnesota

Retrospective examination of echocardiograms was performed in 34 patients with endocardial cushion defects who have undergone cardiac catheterization to determine whether or not partial and complete forms could be differentiated. Eighteen patients with a ventricular septal defect were classified as having complete atrioventricular canal (CAVC), and 16 patients without as partial atrioventricular canal (PAVC). Patients with CAVC had continuous mitral and tricuspid valves (14/18), normal ventricular septal motion (11/14), disorganized mitral valve anterior leaflet (MVAL) echoes (12/17), and normal systolic mitral valve motion (16/16). Findings characteristic of PAVC were timing differences in opening and closure of mitral and tricuspid valves (13/13), paradoxical ventricular septal motion (13/16), definite E and A waves on the MVAL (13/14), and late systolic anterior motion of the mitral valve (12/16). Using mitral-tricuspid continuity or timing differences, 27 of 31 patients could be correctly diagnosed as CAVC or PAVC. When combined with other findings, 31 of 34 patients could be differentiated. Two patients with CAVC had a mitral-tricuspid timing difference and normal MVAL echoes. They were indistinguishable from the PAVC patient with normal ventricular septal motion and systemic right-sided pressures. Mitral insufficiency did not abolish paradoxical ventricular septal motion in our PAVC patients.

CONTRAST ECHOCARDIOGRAPHY IN PARTIAL ANOMALOUS PULMONARY VENOUS RETURN.

Delores Danilowicz, MD,FACC; Itzhak Kronzon,MD. New York University Medical Center; New York, New York.

The diagnosis of partial anomalous pulmonary venous return (PAPVR) in association with a significant left to right atrial shunt is often difficult without the use of dye dilution curves which are tedious and require an arterial line.

Use of contrast echocardiography (ECHO) with injections into the pulmonary vein (PV), left atrium (LA) and inferior vena cava (IVC) proved to be a rapid and apparently successful method of diagnosing PAPVR providing no right to left shunt was present. In 16 children and 4 adults, IVC injections revealed no right to left atrial shunt, i.e. clouding occurred in the right ventricle (RV) only. In 16 patients, PV and LA injections were similar, showing clouding of both left and right heart structures, thereby indicating normal PV drainage with left to right shunting. In 2 children and 2 adults, although LA injections showed clouding of both left and right heart structures, injections into the right PV showed clouding of only the RV, indicating PAPVR. To date, surgical confirmation has been obtained in all four cases of PAPVR and in 12/16 cases with normal drainage (4 still awaiting surgery). An additional child had PAPVR diagnosed in association with a ventricular defect and this was confirmed at surgery also.

The diagnosis of PAPVR can therefore be easily made by use of contrast ECHO providing no right to left atrial shunt exists.

WEDNESDAY, MARCH 8, 1978
AM
BASIC SCIENCE INVESTIGATION—II
8:30 to 12:00

ANATOMIC EVIDENCE FOR LONG-TERM REDUCTION OF INFARCT SIZE BY HYALURONIDASE.

Robert A Kloner, MD, Peter R Maroko, MD, FACC, Eugene Braunwald, MD, FACC. Depts Med, Harvard Medical School & Peter Bent Brigham Hosp, Boston, MA.

Hyaluronidase (H) is a promising intervention for protecting ischemic myocardium but the extent by which it reduces the ultimate size of a myocardial infarct is unknown. Hence, 18 open chest dogs were randomized into 10 controls which received saline and 8 untreated dogs which received hyaluronidase (500 NF units/kg I.V.) 15 min, 2 and 24 hrs after left anterior descending coronary artery occlusion (CAO). Regional myocardial blood flow (RMBF) was measured 10 min after CAO using the microsphere technique. The dogs were allowed to recover, and 3 weeks later, the hearts were excised and anatomic infarct size was determined by cutting the hearts into 1 cm. slices, incubating them in triphenyl tetrazolium chloride which clearly differentiates viable and necrotic tissue and performing planimetry. In the control dogs, 23.2±2.0% of the left ventricle was infarcted compared to only 9.0±2.8% ($p<.001$) in the H-treated dogs. In the control dogs RMBF in the viable myocardium directly adjacent to the infarct was normal (0.98±0.11 ml/min/g) i.e., identical to that found in viable tissue at considerable distance from the infarct; however, in the H-treated dogs it was reduced to 0.64±0.07 ml/min/g, $p<0.05$. This indicates that this tissue, at least in some part, was in jeopardy immediately following CAO but was salvaged by H.

Thus, H resulted in substantial and long-term preservation of the ischemic myocardium. A border zone of viable tissue in which blood flow was lower than normal but in which the myocardium was viable was defined in the hyaluronidase-treated group.

EPICARDIAL BLOOD FLOW DURING CORONARY OCCLUSION STUDIES BY HIGH SPEED CARDIOTHERMOGRAPHY (HSCT)

Dan Tzivoni, MD; Alain Cribier, MD; Katsuo Kanmatsuse, MD; Christopher Chew, MD; Gary Totten, BS; William Ganz, MD, FACC, Cedars-Sinai Medical Center, Los Angeles, Ca.

When exposed to ambient air, the heart loses heat and its epicardial temperature (t) becomes flow dependent. HCST was used to identify the extent and degree of epicardial cooling following reduction of coronary blood flow (CBF) in 16 open chested dogs. The area of ischemia was easily identified by the dark color, reflecting lower epicardial t. Differences in t could be accurately identified (±.2°C) by isotherm analysis. 6 unipolar ECG leads were sutured to the epicardium 2-3 mm apart, between the normal and the ischemic zone. Following complete occlusion of LAD, a cold area was detected within 10". Within 30" the ischemic area reached its full size. Myocardial cooling was 3-4° C from control state and reached its lowest value within 3-4 min. The zone of myocardial cooling corresponded precisely in all dogs with the ischemic area detected by ECG. ST elevation at border zone was 2.3 mm while in ischemic zone was 5.3. Cooling of the epicardium was seen when CBF was reduced beyond 40-50%. This coincided with the ECG ST elevation. Further decrease of CBF increased the size of ischemic zone. Between 70-100% of CBF reduction the size of ischemic zone did not change although there was a slight further drop in the t at complete occlusion. The border of ischemia was sharp with no transition zone with intermediate t. In 5 additional dogs 1-2 mg of methoxamine was given following complete CAD occlusion. A reduction in size of cold area was clearly seen with warming of epicardial surface, accompanied by reduction in magnitude and zone of ST elevation. It is concluded: 1) changes in epicardial t are sensitive indicators of myocardial ischemia. 2) HSCT is a sensitive method to assess the degree and extent of myocardial ischemia.

EVIDENCE FOR A BIEXPONENTIAL, PERFUSION MODEL OF CPK ELIMINATION

C. Jeffrey Carlson, M.D., Bianka Emilson and Elliot Rapaport, M.D., Cardiovascular Research Institute and Department of Medicine, University of California, San Francisco, and Cardiology Laboratory, San Francisco General Hospital, San Francisco, Ca.

CPK elimination by the RE system generally is treated as a single compartment, monoexponent (ME). This assumes that the fraction of CPK in the RE is small, removed as it enters, such that the elimination curve is log linear. However, if CPK clearance is much less than RE flow, then the distribution phase may add to elimination making it biexponential. We studied 10 awake dogs during constant infusion and after single injections of MM-CPK isoenzyme. In six, a priming dose was given with infusion maintained for 320 min. Hepatic venous and arterial blood were sampled from implanted cannulas. Hepatic blood flow (EHBF) was estimated by BSP method. Mean EHBF was 617±74 cc/min (se) with CPK clearance of 7.6±3.4 cc/min. In four, elimination curve was determined from arterial samples for 400 min after a single injection. The elimination curve was analyzed using a biexponential, perfusion model. CPK clearance was 10.2±2.4 cc/min with an effective RE volume of 5±1 L. The half-life (t 1/2) of distribution phase was 41±12 min and the t 1/2 of elimination was 228±99 min. In comparison, t 1/2 of elimination with a monoexponent was 102±12 min. We conclude: 1) clearance is much less than EHBF indicating that distribution may add to elimination; 2) large effective RE volume may indicate partitioning of CPK in the RE system; 3) t 1/2 of elimination using a biexponential model is much longer than that using a monoexponential model ($p < .05$), which poses a serious problem when calculating infarct size by the usual method.

SYSTEMIC AND CORONARY HEMODYNAMIC EFFECTS OF RENIN-ANGIOTENSIN SYSTEM INHIBITION IN SODIUM-DEPLETED DOGS

Chang-seng Liang, MD; Haralambos Gavras, MD; William B. Hood, Jr., MD, FACC, Boston University School of Medicine and Thorndike Memorial Laboratory, Boston, Massachusetts.

The systemic and coronary circulatory effects of teprotide (0.5 mg/kg, i.v.), an angiotensin converting enzyme inhibitor, and saralasin (0.05 to 0.5 µg/kg/min), an angiotensin antagonist, were studied in 14 conscious dogs after sodium depletion for 5 days. Cardiac output (CO, ml/kg/min), heart rate (HR, bpm), mean aortic pressure ($\overline{Pa}$, mm Hg), coronary blood flow (CBF, ml/100g/min), and total peripheral and diastolic coronary vascular resistances (TPVR and CVRd, dyn·s·cm^{-5}, x 10^{-3}) before and 20 min after administration of teprotide or saralasin were:

	CO	HR	$\overline{Pa}$	CBF	TPVR	CVRd
Control	163±4	76±8	116±6	69±5	6.6±0.7	96±7
Teprotide	198±11*	81±12	96±5*	120±13*	4.7±0.6*	48±10*
Control	147±14	79±7	114±6	77±7	6.0±0.6	77±11
Saralasin	163±13*	81±8	94±7*	91±8*	4.8±0.5*	55±5*

(data shown as means±SE; *P<0.05, compared to control)

Left ventricular end-diastolic pressure, dP/dt, dP/dt/P, myocardial O_2 consumption and mechanical efficiency did not change. Similar administration of teprotide or saralasin produced no effects in dogs on regular sodium diet. Plasma renin activity was higher in sodium-depleted dogs (18±5ng/ml/hr) than in control dogs (6±2ng/ml/hr). These results suggest that 1) the renin-angiotensin system exerts vasoconstrictor effects on coronary vasculature during sodium depletion; and 2) the increase in CO after renin-angiotensin system inhibition probably is related to the reduced $\overline{Pa}$, while cardiac contractility and energetics were not affected.

LONG-TERM PRESERVATION OF ISCHEMIC MYOCARDIUM BY IBUPROFEN AFTER EXPERIMENTAL CORONARY ARTERY OCCLUSION.

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Glucocorticoids are anti-inflammatory agents which preserve ischemic myocardium but repeated doses thin the remaining myocardial scar. The goal of this investigation was to determine whether Na-Ibuprofen (IB), a non-steroidal anti-inflammatory drug, exhibits the same beneficial effects as glucocorticoids in preserving the ischemic myocardium without the adverse effect of impeding proper scar formation. Thus, IB (12.5 mg/kg IM), a potent inhibitor of prostaglandin-mediated components of inflammation, was given 5 min, 3 and 6 hrs following left coronary artery occlusion (O) in 98 rats (IB-rats) while another 94 served as controls (C-rats). Two days after O, the left ventricular (LV) myocardium preserved (PM), calculated by total LV creatine kinase activity was 45.8±2.0% of normal in C-rats (n=25) and 23.8±6.3% greater, i.e., 56.7±2.9% of normal ($p<.0025$) in IB-rats (n=20). Also, 2 days after O, PM, by planimetry of histologic sections (hematoxylin-eosin stain) of serial slices of LV, was 49.9±3.2% of normal in C-rats (n=20) and 17.2±5.4% greater, i.e., 58.5±2.7% of normal ($p<.025$) in IB-rats (n=36); after 21 days, it was 54.8±1.7% of normal (n=49) in C-rats and 20.2±4.7% greater, i.e., 65.9±2.6% of normal ($p<.0005$) in the IB-rats (n=42). At 21 days, scar thickness was 0.63±0.03mm in C-rats and 0.67±0.04mm in IB-rats (NS). Thus, direct measurements show that acutely ischemic myocardium can be preserved long-term by multiple doses of IB without thinning the myocardial scar.

PARTIAL PROTECTION OF MITOCHONDRIAL ENERGY PRODUCTION IN ISCHEMIC MYOCARDIUM BY IN VIVO INFUSION OF RUTHENIUM RED PLUS GLUTAMATE AND SUCCINATE.

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Reperfusion of acutely ischemic myocardium is associated with deficient energy production & abnormal Ca^{2+} accumulation. This study evaluates mitochondrial energy production by ischemic reperfused myocardium following an in vivo infusion of a Ca^{2+} antagonist, ruthenium red (RR) and based on previous in vitro studies, in vivo infusion of glutamate (G) & succinate (S). Twenty-five pigs had occulusion of the LAD coronary artery for 2 hrs followed by 2 hrs reperfusion. Seven pigs served as controls; 10 pigs received a bolus of 2 mg/kg RR 15 minutes prior to reperfusion followed by intravenous drip of 0.12 mg/kg/min; 8 pigs received a bolus of 200 mg/kg G&S in addition to RR prior to the reperfusion and followed by intravenous drip of 1 mg/kg/min. Mitochondria were isolated from normal (N) and ischemic reperfused (IR) myocardium. ATP production (n moles) and mitochondrial O_2 consumption (QO_2, ng atoms O/mg/min) was measured and results are shown:

Mitochondria	ATP Formation		QO_2	
(IR)	27 ± 13		7 ± 4	
(IR with RR)	158 ± 38	.02>p	22 ± 6	.01>p
(IR with RR, G&S)	216 ± 60		44 ± 20	
(N)	293 ± 42		281 ± 59	
(N with RR)	272 ± 25		241 ± 60	
(N with RR, G&S)	284 ± 34		250 ± 33	

There was a significant increase in ATP formation and QO_2 in mitochondria from ischemic myocardium reperfused with RR. G&S with RR further stimulates mitochondrial QO_2 and ATP production. Thus, RR plus G&S result in improvement of mitochondrial energy production from ischemic reperfused myocardium.

METABOLIC CONTROL OF MEMBRANE PERMEABILITY FOR CELLULAR PROTEINS STUDIED IN HEART CELL CULTURES DURING SEVERE HYPOXIA.

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The release of cytosolic proteins from heart cells during hypoxia (H) is a well-known phenomenon, generally observed in jeopardized myocardium. Using cultured monolayers of heart cells, prepared by dissociation of neonatal rat hearts with collagenase, the effect of oxygen (O_2) deprivation on membrane permeability for cytosolic enzymes was investigated. The release of creatine kinase (CK) and α-hydroxybutyrate dehydrogenase (α-HBDH) was measured. The cultures were incubated in an O_2-free balanced salt solution for periods up to 23 h. Hereaftermedium and cells were analysed for protein content and CK and α-HBDH activities. Five series of experiments were done: I. with H only, II. H + 5 mM pyruvate, III. H + 5 mM glucose (G), IV. H + 5 mM G + 10^{-5} M iodoacetamide (an inhibitor of glycolysis) and V. O_2 + 5 mM G. Based on medium α-HBDH activity it was calculated that the cells in the series I, II and IV had released 96, 95 and 97 % respectively of their original activity (1.1-1.4 IU/culture) into the medium in 23 h. In both series III and V only 17 % of cellular α-HBDH was released in 23 h. There was excellent correlation (r=0.99) between % α-HBDH released and % CK released during H. It is concluded, that during O_2 deprivation membrane integrity is well maintained in cultured heart cells, only if glycolysis is active.

CALCIUM TRANSPORT ATPASE OF CARDIAC SARCOPLASMIC RETICULUM IN EXPERIMENTAL HYPERTHYROIDISM

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Increased "calcium pump" activity of the cardiac sarcoplasmic reticulum (SR) has been reported in experimental hyperthyroidism. SR isolated from the hearts of hyperthyroid (HT) rats had increased Ca^{++} uptake (101 ± 3.6 vs 70 ± 2.1 n moles Ca^{++}/mg/min, $p<0.01$), Ca^{++} binding (96 ± 1.8 vs 68 ± 1.9 n moles Ca^{++}/mg/min, $p<0.01$) and Ca^{++} ATPase (53 ± 3.9 vs 37 ± 2.0 n moles P_i/mg/min, $p<0.01$). In order to gain further insight into the mechanisms responsible for these differences, the kinetics of the cardiac Ca^{++}-transport ATPase were studied. The steady-state levels of a phosphoprotein intermediate [EP] formed during ATP hydrolysis were higher for microsomes from HT rats (1.4 ± 1.2 n moles/mg/min vs 1.7 ± 0.1 n moles/mg/min). The Ca^{++} concentration required for half-maximal stimulation of both [EP] formation and ATPase activity was 1.6 ± 0.1 μM for HT and 4.9 ± 0.2 μM for euthyroid (ET) microsomes. The apparent Km for MgATP, pH optimum and turnover rates of the transport ATPase (calculated as the ratio of [EP] to ATPase activity) were unchanged by hyperthyroidism. The passive permeability of microsomal vesicles to Ca^{++} was enhanced in the preparations from HT animals and was associated with altered lipid composition of the SR. Phospholipid content was increased (0.56 mg/mg protein vs 0.42 mg/mg protein in ET rats, $p<0.01$). The fatty acid composition of the phospholipids was also changed mainly due to an increase in palmitate and stearate coupled with decreases in arachidonate and linoleate levels. These results may partly explain the altered Ca^{++} transport function of the SR in experimental hyperthyroidism.

TIME-DEPENDENT CHANGES IN Ca RELEASE FROM EGTA-TREATED SARCOPLASMIC RETICULUM

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Changing rates of Ca release from Ca-filled SR vesicles have been observed after inhibition of the Ca pump by the Ca-chelator EGTA. Three phases of Ca release were seen when 1-10 mM EGTA was added during Ca uptake by 6-10 μg/ml rabbit skeletal SR protein, in 120 mM KCl, 40 mM histidine buffer (pH 6.8), and 5 mM MgATP, where 50 mM phosphate was the Ca-precipitating anion. A brief (< 15 sec.) release of approximately 50-100 nmol/mg Ca was followed by a marked slowing of Ca release that lasted 60-90 sec., after which 2-3 μmol/mg Ca were rapidly released. Approximately 25% of the intial Ca taken up remained in the vesicles after > 1 hour. The timing of this sequence of changes in Ca release rate was not influenced by the final level of outside Ca^{2+} after addition of 75 μM or 1.5 mM EGTA. Early slowing of Ca release rate was not seen after EGTA addition when Ca influx rate had spontaneously slowed and Ca efflux increased later during ATP-supported Ca uptake reactions. When the initial Ca uptake reaction was carried out in 10 mM acetyl-P instead of ATP, changes in release rate were much less marked, but reduction of ATP from 5 mM to 5 μM (Mg^{2+} = 0.37 mM) did not markedly influence the time-dependent release rate changes. These findings are consistent with the view that a shift in Ca pump sites from a "pump" to a "release" mode occurs during the Ca uptake reaction. The changes in Ca release rate observed after EGTA addition may reflect the operation of an ionic "gating" mechanism in the SR membrane.

POTASSIUM-DEPENDENT EXOCYTOSIS OF NOREPINEPHRINE FROM HYPOXIC CANINE CORONARY ARTERY

Philip D. Henry, MD, FACC, Leonor Borda, MD, Washington University, St. Louis, Missouri

Potassium (K+), like other depolarizing stimuli, promotes exocytosis of norepinephrine (NE) from sympathetic nerves. To determine whether discharge of cellular K+ from hypoxic arteries underlies the release of NE, canine coronary arteries (n = 21) were mounted for recording of isometric force and equilibrated with buffer containing ^{3}H-NE(10^{-7} M) and ^{42}K(4 mM). Subsequently, arteries were superfused with oxygenated buffer containing no NE and cold K+, and radioactive effluxes were monitored. Sudden superfusion with de-oxygenated buffer evoked transient arterial relaxation and subsequent contracture accompanied by fifteenfold and five fold increases in ^{42}K and ^{3}H efflux. During contracture, 10^{-7} M propranolol relaxed the artery without altering ^{42}K or ^{3}H efflux, indicating that contracture was β-mediated, that K+ release was not enhanced by high arterial tone, and that propranolol had no effect on NE release. Colchicine, a blocker of exocytosis, inhibited ^{3}H-efflux, relaxed the artery, but did not affect ^{42}K-efflux, indicating that ^{42}K-efflux was not increased by noradrenergic stimulation. Proadifen (SKF 525A), an inhibitor of transmembrane K+ flux, inhibited ^{42}K and ^{3}H-efflux, and relaxed the artery. During sustained hypoxia and proadifen-suppressed ^{42}K-efflux, ^{3}H-efflux was augmented by exogenous K+ (10 mM), indicating that proadifen decreased ^{3}H-efflux indirectly by inhibiting hypoxic discharge of K+. Assay of ^{3}H-NE and of the activity of dopamine β hydroxylase in the effluents paralleled total ^{3}H-efflux in all experiments. Thus, hypoxic release of NE is mediated by active, K+-stimulated exocytosis and does not represent passive leakage of neurotransmitter from hypoxic nerves.

DOES NOREPINEPHRINE PRODUCE MYOCARDIAL CELLULAR HYPERTROPHY AND OR NECROSIS?

Gerald Adomian, PhD; Ernest Haeusslein; Michael M. Laks, MD, FACC, Division of Cardiology, Harbor General Hospital, UCLA School of Medicine, Torrance, California

In contrast to hypertrophy produced by a pressure overload, we have demonstrated that the number of widened and multiple intercalated discs, and the presence of widened Z bands do not increase with subhypertensive norepinephrine (NE) infusion. Therefore, the purpose of this study was to demonstrate whether a subhypertensive dose of NE increases myocardial cell size, the index of myocardial hypertrophy. After 4 months of infusion of NE in the conscious dog, tissue was taken from the free lateral wall at the bases and apices of the LV and RV (LB,LA,RB,RA) and processed for light and electron microscopy. Cell lengths were measured on 50 cells from the areas sampled from 7 normal and 8 experimental hearts. After NE infusion, LV and RV weights increased ($p<0.001$) and cell lengths increased, the bases greater than the apices ($P<0.01$). The mean cell lengths ± SEM for the normal LB,LA,RB and RA were as follows: 79±2.2, 74± 6.4, 80±1.3, and 74±2.5 microns. After NE infusion cell lengths increased: 99±2.1, 86±2.1, 96±3.8, and 85±3.5 microns, resp. ($p<0.001$). LV and RV weights for the normal dog were 55±1.4 and 34±1.6 grams, resp. After NE infusion, LV and RV increased to 69±4.1 and 38±2.0 grams, resp. Of importance, no myocardial necrosis, fibrosis or cellular infiltration was seen. In conclusion, subhypertensive doses of NE produced myocardial cellular hypertrophy. These observations support the hypothesis that NE may be a myocardial cellular hypertrophying hormone, and suggests that low dose NE hypertrophy may be "physiological" rather than "pathological".

REGRESSION OF ATHEROSCLEROSIS DURING CHOLESTEROL FEEDING IN *Macaca fascicularis*

M.Rene Malinow, MD; Phyllis McLaughlin, BA; Herbert K. Naito, PhD; and Lena A. Lewis, PhD, Oregon Regional Primate Research Center, Beaverton, Oregon

Monkeys fed a semipurified diet (SPD) containing 1.2 mg of cholesterol/Cal for 6 months were stratified according to plasma cholesterol and randomly assigned to four groups of 18 animals each. Group (a) was killed (end of induction). For the next 18 months, group (b) received SPD, and group (c) received SPD + 50% alfalfa meal (both diets contained 0.34 mg of cholesterol/Cal); group (d) was fed laboratory monkey chow. At the end of the observation period, plasma cholesterol (mg/dl) was: (a) 701 ± 51 (mean ± S.E); (b) 287 ± 23; (c) 163 ± 7; and (d) 139 ± 4. Aortic atherosclerosis (A) (1 to 5) was: (a) 3.8 ± 0.3; (b) 3.7 ± 0.3; (c) 1.8 ± 0.2; and (d) 1.8 ± 0.2. Coronary A (% encroachment) was: (a) 23.0 ± 5.1; (b) 14.6 ± 2.9; (c) 5.8 ± 1.3; and (d) 7.6 ± 1.9. Thus, the cholesterol-containing SPD with alfalfa and the chow diet without added cholesterol both induced regression of aortic and coronary A. Alfalfa was probably effective through inhibition of cholesterol absorbtion by alfalfa saponins, since we have demonstrated the existence of such a mechanism in rats. The present results suggest that regression of atherosclerosis could be obtained in man even without greatly reducing cholesterol intake.

WEDNESDAY, MARCH 8, 1978
AM
CHRONIC ISCHEMIC HEART DISEASE
8:30 to 12:00

REVERSAL OF EXERCISE-INDUCED HYPOTENSION FOLLOWING CORONARY ARTERY BYPASS

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Exercise-induced hypotension is an ominous prognostic sign for patients with coronary heart disease. We analyzed the exercise responses following myocardial revascularization in 23 patients who experienced exertional hypotension during Standard Bruce Maximal Multistage Treadmill Tests. Coronary bypass was performed within four months (mean 1.5 months) of initial tests and retesting was done two to nine months (mean 4.5 months) postoperatively.

	Preop	Postop
Mean change systolic blood pressure (mmHg)	-22	+36
Mean change in heart size (beats/min.)	+56	+81
Mean rate-pressure product	188	295
Mean exercise duration (min.)	4.4	7.8
Mean functional aerobic impairment	46%	6%

While all patients had multiple vessel disease and exercise-induced myocardial ischemia, only two had poor ventricular function at rest (ejection fraction < 0.4). This suggests that exercise-induced hypotension was more often associated with temporary ischemia than with permanent myocardial damage. After revascularization 20/23 or 93% of patients showed a positive blood pressure response to exercise. There were two intra-operative infarcts and no postoperative infarcts or deaths (mean follow-up 21 months). Exercise-induced hypotension in patients with obstructive coronary atherosclerosis is usually a manifestation of reversible ischemic left ventricular dysfunction which can be corrected by successful myocardial revascularization.

LONG TERM EFFECTS OF CORONARY SURGERY VERSUS MEDICAL THERAPY ON EXERCISE PERFORMANCE

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The effects of coronary surgery on exercise performance have been documented only for short term follow up. Five years after entry into a prospective, randomized trial, exercise performance was assessed in 25 surgically (S) and 13 medically (M) treated patients with stable angina pectoris, equivalent in age, functional class and extent of angina, medications, treadmill ST-segment change, and number of diseased vessels. Propranolol was discontinued prior to testing. Exercise tolerance time in seconds (T), maximum heart rate (HR), and peak double product (DP) were observed in symptom-limited treadmill testing at 0, 1, and 5 years.

	0			1*			5 years*		
	T	HR	DP	T	HR	DP	T	HR	DP
M	253 ±35	130 ±5	219 ±16	229 ±24	119 ±4	195 ±9	264 ±26	117 ±5	177 ±14
S	306 ±32	136 ±5	217 ±19	357 ±27	144 ±4	232 ±11	382 ±28	139 ±5	230 ±14

(mean ± S.E.M.; *$P<0.05$)

M and S were similar at entry. At 5 years, T, HR, and DP were significantly higher in S. At 5 years, S had significantly improved in T and DP.

We conclude that improved exercise performance after coronary surgery is maintained in late follow up, and is superior to maximal exercise performance in comparable, medically treated controls. These data confirm and supplement previously published results.

PROSPECTIVE RANDOMIZED STUDY OF CORONARY BYPASS SURGERY FOR CHRONIC STABLE ANGINA.

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One hundred patients (pts) are entered in a randomized study comparing medical (M) and surgical (S) therapy for stable disabling angina. Initial clinical and angiographic data are similar in the two groups. Initially, all pts were in Functional Class (FC) III.

Critical events in 49 M and 51 S pts, followed 7 to 69 months (mean 36 mos), are: death - 5 in M, 4 in S; new infarction - 8 in M, 6 in S; high risk unstable angina requiring operation - 7 in M and 3 in S (differences not significant). Use of actuarial techniques shows no difference in survival between M and S treatment in pts with one, two and three vessel disease. FC improved significantly in S pts after 6 months.

Graded exercise stress testing (GXT), pacing tachycardia (PT), coronary and left ventricular (LV) angiography have been completed on entry and 6 mos later in 45 M and 45 S pts. GXT remained positive at 6 mos in 58% of M and S pts, however, the S pts achieved a significantly higher work load (mean ± SE, pre-op 388 ± 29 vs 633 ± 31 KPM at 6 mos, $p<.01$). Heart rate at angina during PT was also higher at 6 mos in S pts (125 ± 3 vs 141 ± 4 beats/min, $p<.01$) but was essentially unchanged in M pts. Mean LV ejection fraction and LV end-diastolic pressure showed no significant change after 6 mos in both M and S pts.

Functional improvement has occurred in both groups but the extent and frequency are greater with S therapy. The improvement in FC in S pts is corroborated by objective testing. There are no significant differences in mortality, morbidity or LV function at this point in the study.

UNSTABLE ANGINA PECTORIS - NATIONAL RANDOMIZED STUDY OF SURGICAL VS MEDICAL THERAPY: RESULTS IN LEFT ANTERIOR DESCENDING DISEASE.

Richard O. Russell, Jr., M.D., FACC; Leon Resnekov, M.D.; Michael Wolk, M.D.; Robert Rosati, M.D.; C. Richard Conti, M.D.; Lewis C. Becker, M.D.; Adolph M. Hutter, Jr. M.D.; Theodore Biddle, M.D.; John S. Schroeder, M.D.; Edward M. Kaplan, M.D.; John P. Gilbert, M.D.; Michael B. Mock, M.D. University of Alabama, Birmingham, Alabama

The therapeutic implications of left anterior descending (LAD) disease remains unsettled. Of the 288 patients (pts) randomized to maximal medical (Med) or surgical (Surg) therapy, 202 had LAD disease > 70% and were followed for a mean of 2 years. Pts were divided into 3 categories based on location of disease in reference to the first septal perforator: proximal, distal or both.

Results:

		Mortality			
		Proximal	Distal	Both	
Med	(102)	3/47	3/36	2/19	N.S.
Surg	(100)	7/41	4/36	1/23	
		Myocardial Infarction			
		Proximal	Distal	Both	
Med	(102)	8/47	1/36	1/19	N.S.
Surg	(100)	13/41	5/36	5/23	

Pts with proximal disease or both had more Angina Class II-IV with Med (41) than with Surg (7), $p < .01$. At last follow up, more Med than Surg pts were working.

Conclusion: Comparing Med vs Surg, there was no difference at 2 years in mortality or MI rate in pts with LAD disease, regardless of location. However, angina was more prevalent in the Med patients.

OBJECTIVE EVIDENCE FOR THE COMPARATIVE BENEFITS OF SURGICAL VERSUS MEDICAL THERAPY FOUR YEARS AFTER RANDOMIZATION OF PATIENTS WITH STABLE ANGINA PECTORIS

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Therapy for stable angina pectoris was assessed by symptom-limited cycle ergometry (E) before and annually for 4 years (yrs) after randomization (R) of 16 patients (pts) to surgical (S) and 21 pts to medical (M) therapy. Before R, the M and S groups were almost identical in age, 50±1 yrs, coronary anatomy, myocardial function, and the mean maximal E endpoints of heart rate (HR), work load (WL), oxygen uptake and heart rate x systolic blood pressure/100 (RPP). Mean values (±SE) were:

		Pre-R	No. Yrs Post-R			
			1	2	3	4
HR	M	132±6	130±7	118±6*	118±6	112±5**
(beats/min)	S	137±6	149±4†	135±4†	122±6	127±5†
WL	M	498±35	457±42	391±33**	391±30*	382±25**
(KPM)	S	550±37	589±33†	525±26†	463±20	453±26†
MVO_2	M	16.8±0.9	15.6±1.2	14.1±1.0**	13.8±0.9**	13.0±0.8**
(ml/Kg/min)	S	18.5±1.1	19.2±1.0†	16.9±0.7	14.7±0.7*	14.6±0.7**
RPP	M	226±31	186±13	184±28	175±20	165±28*
	S	283±23	240±25	252±10	–	240±27

vs. pre-R, * $p<0.05$, ** $p<0.005$; M vs. S, † $p<0.05$

After R, S pts maintained their HR and WL over 4 yrs while MVO_2 declined at 3 and 4 yrs. In contrast, M pts showed significant decrease in HR at 2 and 4 yrs, WL at 2, 3 and 4 yrs and RPP at 4 yrs. Comparisons between S and M pts post-R showed significantly higher HR, WL and MVO_2 at 1 yr and HR and WL at 2 and 4 yrs in S group. The 10 S pts known to have patent grafts were not materially different from the total S group compared to M pts. At 4 yrs 15 of 21 M pts (71%) and 8 of 16 S pts (50%) had ischemic ECG changes at the end of exercise. In these pts with stable angina pectoris, M therapy failed to prevent the continuing deterioration in all annual E parameters for 4 yrs. In contrast, S therapy maintained the pre-R E performance as measured by HR, WL and RPP.

UNSTABLE ANGINA PECTORIS-NATIONAL RANDOMIZED STUDY OF SURGICAL VS. MEDICAL THERAPY: RESULTS IN PRINZMETAL TYPE ANGINA

John S. Schroeder, MD, FACC; Richard O. Russell, Jr., MD, FACC; Leon Resnekov, MD; Michael Wolk, MD; Adolph M. Hutter Jr., MD; Robert A. Rosati, MD, C. Richard Conti, MD; Lewis C. Becker, MD; Theodore Biddle, MD; Edward M. Kaplan, MD; John P. Gilbert, MD; Michael B. Mock, MD, Cardiol. Div., Stanford Med. Ctr., Stanford, California.

A prospective study randomized 288 patients (pts) hospitalized with unstable angina to surgical (Surg-141 pts) or maximal medical therapy (Med-147 pts). Study criteria were transient ST-T changes during pain (90% had rest pain), >70% narrowing of 1,2 and 3 vessels, suitable distal vessels and ejection fraction >30%. Main left disease was excluded. During pain, 79 pts (27.4%) had documented ST elevation, presenting a unique opportunity to compare Med vs Surg therapy for Prinzmetal type angina in a randomized study. Results during a mean 24 month follow-up are:

	No. of pts	In-hospital MI	In-hospital Death	Late MI	Late Death	Late angina class I	II	III	IV
Med	42	4	2	7	1	10	15	8	0
Surg	37	5	2	3	3	26	2	0	1

Mortality and myocardial infarction (MI) rate did not differ significantly between Med and Surg groups. Class II-IV angina was more frequent in Med pts ($p<.001$). However, work status during follow-up did not differ. We conclude that urgent coronary bypass surgery for Prinzmetal type unstable angina did not affect mortality, infarction rate, or work status but was associated with improved subsequent angina class.

HYDRALAZINE-INDUCED ISCHEMIA WITHOUT TACHYCARDIA: THE IMPORTANCE OF CORONARY PERFUSION PRESSURE GRADIENTS
Milton Packer, MD; Jose Meller, MD, FACC; Richard Gorlin, MD, FACC; Louis Teichholz, MD, FACC; Michael Herman, MD, FACC, Mount Sinai Hospital, New York, New York.
Although hydralazine (H) may provoke ischemia by reflex tachycardia, patients (pts) with heart failure (CHF) receiving H to decrease (↓) afterload show no changes in heart rate (HR), yet ischemic events do occur. To clarify the mechanism, 100 mg oral H was given to 8 pts with CHF, 4 with ischemic (ICM) and 4 with nonischemic cardiomyopathies (NICM). Thermodilution cardiac index (CI) (L/min/M^2), HR, arterial diastolic (ADP) and pulmonary wedge pressures (PWP) were determined every 30 min for 4 hrs. The coronary perfusion pressure gradient (CPG), (aortic minus left ventricular pressures in diastole), a major correlate of subendocardial blood flow, was estimated as ADP-PWP. Results (means of 8 pts, ***=p<.001, **=p<.01, *=p<.05):

	0 hrs	1½ hrs	2½ hrs	3½ hrs
CI	2.01	2.68**	3.07***	2.97***
ADP	69.2	57.7***	60.4**	62.7**
PWP	24.6	21.1*	18.9**	21.1*
CPG	44.6	36.6***	41.5	41.6
HR	90	89	88	89

Although the peak CI and maximal ↓ in PWP occurred at 2½ hrs, the lowest ADP was observed at 1½ hrs. This dissociation in timing of maximal effects on ADP and PWP caused disproportionate ↓ in CPG (p<.001) at 1½ hrs; changes in CPG at 2½ hrs and 3½ hrs were not significant despite the persistent ↓ in ADP. No changes in HR were noted. The timing and magnitude of these changes were identical in ICM and NICM. However, 3 of 4 pts with ICM experienced ischemic episodes at 1-2 hrs after H doses, whereas all pts with NICM improved clinically without adverse effects. Conclusion: H causes a transient but marked ↓ in CPG which may provoke ischemia in ICM even without tachycardia.

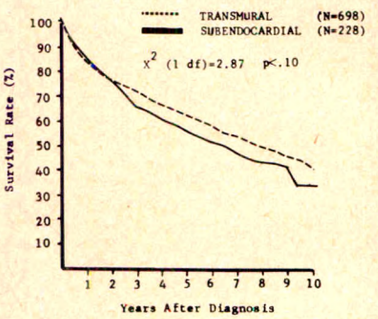
SHORT AND LONG-TERM PROGNOSIS OF TRANSMURAL AND SUBENDOCARDIAL INFARCTION.
Robert J. Goldberg, MS; Harold L. Kennedy, MD, MPH, FACC; Moyses Szklo, MD, MPH, DrPH; and James Tonascia, PhD, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland.

To examine short (in-hospital) and long-term prognosis from transmural and subendocardial infarction, a sample of records of myocardial infarction (MI) patients discharged from 20 Baltimore hospitals were reviewed. Analysis of in-hospital case-fatality rates (CFR) based on 1401 patients discharged from 20 Baltimore hospitals, indicates a CFR among patients diagnosed with a transmural infarction of 26.8% (255/953) with a corresponding CFR of 19.7% (56/284) in patients with a subendocardial infarction ($P < .05$). These differences did not disappear when rates were adjusted for age, sex, MI order, location of MI, admission to coronary care unit and anticoagulant therapy.

Long-term survival was then assessed in the transmural and subendocardial groups comprising 698 and 228 hospital survivors respectively. A life-table approach was utilized and respective survival curves plotted as shown.

As seen, a lower ($P < .10$) survival rate was demonstrated among hospital survivors with a subendocardial infarction over a ten-year follow-up period.

With the current interest in limiting the size of the acute myocardial infarction which may predispose to the development of subendocardial infarction, these results obtained from a large community-wide study focus attention on the reassessment of subendocardial infarcts in relation to short and long-term prognosis.



EFFECT OF ANTICOAGULATION ON THE INCIDENCE OF MURAL THROMBI AND SYSTEMIC EMBOLIZATION IN PATIENTS WITH LEFT VENTRICULAR ANEURYSMS.
Michael T. Simpson, MD, Albert Oberman, MD, Nicholas T. Kouchoukos, MD, FACC, and William J. Rogers, MD, FACC. U. Ala. Med. Ctr., Birmingham, Ala.

Fifty-eight consecutive patients (pts) post-myocardial infarction (MI) undergoing surgery for left ventricular (LV) aneurysm were studied retrospectively to assess the frequency, characteristics, and complications of mural thrombi found at surgery, and to determine what effect chronic anticoagulation might have had upon the clinical course of these pts. Mural thrombi at surgery were found in 66% (38/58) of the pts. Of these, only 10 (26%) were prospectively identified by LV angiography; conversely, LV angiography misidentified the presence of mural thrombi in 10% (2/20) of pts who had no thrombus at surgery. Pts with mural thrombi were not different from those without thrombi in terms of time elapsed since MI (28±7 vs 24±10 mos), LV end-diastolic pressure (LVEDP)(18±2 vs 18±2 mm Hg), ejection fraction (22±1 vs 25±2%) or angiographic scar size (33±2 vs 29±3%). Of 18 pts chronically anticoagulated with sodium warfarin pre-op, 11 had mural thrombi, whereas 9 did not (p ns). There were only 2 pts in the total group (2/58=3%) with a pre-op event compatible with systemic arterial embolization--1 of these pts was anticoagulated. Survival 30 days post-op was 79% (30/38) in pts with mural thrombus and 90% (18/20) in those without thrombus (p ns). Thus, in pts with post-MI LV aneurysmectomy: (1) the incidence of mural thrombus is high but cannot be reliably identified prospectively by LV angiography or predicted by time since MI, angiographic scar size, ejection fraction, or LVEDP; (2)the incidence of pre-op systemic arterial embolization is very low; and (3) chronic anticoagulation has no apparent effect on incidence of pre-op systemic arterial embolization or incidence of LV mural thrombus at surgery.

LONG TERM COURSE OF SUBENDOCARDIAL MYOCARDIAL INFARCTION COMPARED TO THAT OF ANTERIOR AND INFERIOR TRANSMURAL INFARCTION. A CONTROLLED STUDY

Adolph M. Hutter, Jr., MD, FACC, Lawrence A. Yeatman, MD, Theresa Flynn, RN, Roman W. DeSanctis, MD, FACC, Mass. Gen. Hospital, Boston, Mass.

The long term course of 67 patients (pts) with subendocardial myocardial infarction (SEMI) was compared to that of 66 pts with anterior transmural MI (AMI) and 63 pts with inferior transmural MI (IMI) matched for age (ave 66 yrs), sex (66% males), previous MI (45% of pts) and prior congestive failure (CHF) (18% of pts). Over an average followup of 29 months, no difference was found in angina, syncope, subsequent CHF or work status. Three month survival was better in SEMI (86% vs 71% for AMI and IMI; $p < .02$) but late survival (> 3 months) was worse in SEMI than AMI and IMI such that overall survival was comparable in the 3 groups. SEMI had a higher incidence of subsequent MI compared to IMI ($p < .05$) and especially AMI ($p < .001$). At 9 months, subsequent MI had occurred in 18% of SEMI, 2% of AMI and 2% of IMI ($p < .005$). By 54 months, new MI incidence was 34% of SEMI, 6% of AMI ($p < .001$) and 14% of IMI ($p < .01$). Subsequent MIs tended to occur in same area of original SEMI (9 of 13 pts with sufficient data). Thus, compared to AMI and IMI, SEMI appears to be a more unstable ischemic event reflected in a higher risk of subsequent MI and higher late mortality. More aggressive angiography and therapy (medical or surgical) may be warranted in SEMI.

THE PROGNOSTIC IMPLICATION OF LEFT BUNDLE BRANCH BLOCK IN PATIENTS WITH PROVEN CORONARY ARTERY DISEASE

Robert H. Peter, MD, FACC; John Dixon, MD, Martin J. Conley, MD; Duke University Medical Center, Durham, North Carolina 27710

The prognostic implication of left bundle branch block (LBBB) was evaluated in 66 consecutive patients (PTS) who underwent selective coronary arteriography and left ventriculography for suspected coronary artery disease (CAD) and followed prospectively from 6 months to 8 years. Fourteen PTS had normal coronary arteries and 52 had proven significant CAD defined as > 75% diameter narrowing of one or more major coronaries. The 2 yr mortality rate calculated by life table method in the 14 normals was 0% while the 2 yr mortality rate in the 52 with significant CAD was 37% in 14 pts undergoing aortocoronary bypass surgery and 55% in 38 PTS treated medically. Among the 38 medical PTS with significant CAD, 31 had at least one of three high risk characteristics (3 vessel CAD, left main coronary obstruction, or diffuse poor ventricular contraction) with a 2 yr mortality rate of 65%. Nine of the 14 surgical PTS with at least one of those three high risk factors had a 2 yr mortality rate of 53%. Twelve (5 surgical PTS and 7 medical PTS) with significant CAD but without any of those three high risk factors, had a 2 yr mortality rate of 0%. It appears that LBBB is a poor prognostic sign in PTS with significant CAD only if 3 vessel CAD, left main coronary obstruction, or diffuse poor ventricular contraction is present.

HEMODYNAMIC AND ELECTROCARDIOGRAPHIC ACCOMPANIMENTS OF RESTING POST-PRANDIAL ANGINA

Jaime Figueras, MD; William Ganz, MD, FACC; Bramah N. Singh, MD, FACC; H.J.C. Swan, MD, FACC, Cedars-Sinai Medical Center, Los Angeles, California

The mechanism of post-prandial angina (PPA) was studied by continuous (average, 21 hrs) monitoring on tape of hemodynamic variables and V_5 lead of the ECG in 10 pts with history ofPPA and exertional angina. Systemic pressure (BP) was measured by a radial artery cannula and pulmonary artery pressure (PAP) by Swan-Ganz catheter. Cardiac index (CI) by thermodilution and stroke index (CI) were measured every 2 hrs, before and 20 mins after each meal (600 calories), and at onset of and following relief of pain by nitroglycerin. When pain did not follow a meal, the only significant changes after a meal were increases in CI (2.20±0.13 to 2.63±0.16 L/min/m^2, $p<0.02$) and SI (32.8±2.0 to 37.0±2.7 ml/beat/m^2, $p<0.05$) with a decrease in systemic vascular resistance (SVR) (1598±100 to 1322±90 dynes/cm/cm^{-5}, $p<0.01$). This suggest a post-prandial increase in myocardial contractility. In contrast, when pain did follow a meal, there was a significant post-prandial increase in BP (91.5±3.8 to 122±8.8 mmHg, $p<0.02$), heart rate (HR) (75 5 to 98 6, p 0.05), PAP diastolic (11.8 0.9 to 29.3 3.0 mmHg, p 0.001), SVR (1678 197 to 2054 200 dynes/sec/cm^{-} , p 0.05) and a decrease in SI (34.1 2.7 to 26.5 2.6 ml/beat/m , p 0.05) at onset of pain, during ischemia. In each instance, PPA occurred within 25 mins, following a meal. Changes in HR began prior to onset of ischemia. However, changes in BP, PAP diastolic and ST depression occurred concomitantly. The data suggest that PPA is probably related to increases in contractility and heart rate resulting in myocardial oxygen demand, and as ischemia develops, left ventricular failure with increased SVR supervenes.

WEDNESDAY, MARCH 8, 1978
AM
SUDDEN DEATH AND AMBULATORY MONITORING
8:30 to 12:00

DAILY TRANSTELEPHONIC ELECTROCARDGRAPHIC MONITORING OF CONVALESCENT MYOCARDIAL INFARCTION PATIENTS

William B. Tuttle, MD, Do Wan Lee, MD, and Clyde D. Schoenfeld, MD, FACC, Shadyside Hospital, Pittsburgh, PA 15232

The early weeks following discharge after myocardial infarction have been identified as a period of high risk for sudden death. There is high correlation of this phenomenon with the incidence of ventricular arrhythmias (VA) recorded sporadically, by Holter Monitoring (HM). In one hundred patients with myocardial infarction transtelephonic electrocardiograms (TTE) were recorded for one minute daily for 21 days after discharge via the Cardio-Beeper (CB). Patients called from their home to the CCU. Extra calls were made in the event of alarming symptoms. Results of TTE were compared with 24 hour HM on the last day of admission and the 21st day after discharge in 50 patients. The TTE detected significant frequencies of PVC's in 37% of patients while a single HM detected this in only 14% ($p<.01$) on the day of discharge and in 16% ($p<.01$) on the 21st day. In 13% of patients TTE detected bigeminy while the two HM found it in 2% ($p<.05$) and 5% (NS). The two methods showed equal sensitivity in detecting pairs of PVC's (5 to 9%) and ventricular tachycardia (one patient). Extra transmissions resulted in treatment of patients for heart failure (2), new chest pain with ST changes (7), and drug intoxication or intolerance (4). One TTE was recorded minutes prior to sudden death. It showed a complex tachycardia. Three patients died suddenly just after termination of the study, two had shown increased PVC's. New VA or failure of anti-arrhythmia drugs were found in 18 persons. These results suggest that daily TTE records are a practical, economical "window" of ECG monitoring in the post-infarction period. They are at least as senitive as sporadic HM, and in many ways superior. The method has potential for evaluating drug therapy and guiding self-administration of drugs.

COMPARISON OF PRACTOLOL AND PROPRANOLOL ON CORONARY OCCLUSION-INDUCED VENTRICULAR FIBRILLATION

David L.Pearle, M.D., FACC; Daniel J. Williford, B.S., and Richard A. Gillis, Ph.D., Georgetown University, Washington, D.C.

A large prospective study has recently demonstrated that the cardioselective beta adrenergic receptor blocking drug practolol decreases long-term mortality in patients after anterior MI. A multicenter study is in progress in the U.S. to determine whether propranolol, a non-cardioselective beta blocker, affords similar protection. The present study was designed to compare the ability of practolol and propranolol to prevent ventricular fibrillation (VF) in experimental anterior MI. Ligation of the left anterior descending and first septal coronary arteries of the dog causes VF in 90% of animals within 30 min. We performed this ligation in controls and in animals pretreated with propranolol (0.5 mg/kg) or with practolol (1.5-2.5 mg/kg). These doses produced nearly equivalent shifts in isoproterenol-induced chronotropic dose response curves, indicating equivalent degrees of beta blockade. Eighteen animals had confirmed ligation without developing cardiogenic shock. All six control animals died in VF. Six of six propranolol pretreated animals fibrillated. None of the six practolol pretreated animals developed VF during the 45 min. post-ligation observation period. Practolol afforded significant protection compared to controls and compared to propranolol treated animals ($p<0.05$). We conclude that practolol protects against VF caused by anterior ischemia in this model, but propranolol does not. The improved survival associated with practolol is probably due to selective beta adrenergic blockade.

TREATMENT OF VENTRICULAR ARRHYTHMIAS AFTER ACUTE MYOCARDIAL INFARCTION WITH PROPRANOLOL Gerald M. Koppes, MD; Frederic G. Jones, MD, FACC; Charles H. Beckmann, MD, FACC, Wilford Hall USAF Medical Center, Lackland AFB TX.

Propranolol (P) treatment of premature ventricular contractions (PVCs) was studied in 19 ambulatory patients (pts) 8 weeks after acute myocardial infarction (AMI). The 19 pts had greater than 30 PVCs/hour with 16/19 also having bigeminy, paired PVCs or ventricular tachycardia. Twenty-two hour ambulatory ECG recording (AR) and Bruce exercise treadmill testing (ETT) were performed baseline, 4-7 days after P administration and repeat baseline 4-7 days after P was stopped. P was administered in doses of 20 mg orally every 6 hours and increased in 80 mg daily increments to control PVC frequency. Total P dose ranged from 80 to 240 mg/day except in 2 pts who received 400 mg daily. ETT induced PVCs were abolished in 6/14 pts with P and the complexity decreased in all but 2 pts. A striking reduction in PVC frequency by AR after P treatment was seen in 16/19 (84%) pts. Average hourly PVC frequency in these 16 pts was reduced by 91% and peak-hourly PVC frequency by 93%. PVC frequency returned to 70% of baseline after P stopped. Side effects were minimal with 6/19 (35%) experiencing mild fatigue or gastrointestinal distress. It is concluded that P effectively suppresses both resting and exercise induced PVCs in the early post-hospital phase of AMI. PVC control in the early high risk period after AMI may be added to the list of ventricular arrhythmias such as those attributed to catecholamines, digitalis intoxication, and hyperthyroidism which can be managed by beta-blocking drugs.

AMBULATORY MONITORING AND EXERCISE STRESS TESTING IN THE MANAGEMENT OF PATIENTS WITH MALIGNANT VENTRICULAR ARRHYTHMIA
Thomas B. Graboys, MD; Regis A. DeSilva, MB, FRCP(C); Bernard Lown, MD, FACC, Cardiovascular Laboratories, Harvard School of Public Health, and Cardiovascular Division, Peter Bent Brigham Hospital, Boston, Mass.

The reproducible exposure of advanced grades of ventricular premature beats (VPBs) is essential for treating infrequently recurring episodes of malignant ventricular arrhythmias (ventricular fibrillation, VF, and ventricular tachycardia with syncope, VTS). While 24-hour monitoring in patients with ischemic heart disease (IHD) provides a higher yield of VPBs, as compared to exercise stress, the precise diagnostic utility of these two methods is uncertain in patients (PTS) with VF and VTS. This question was examined in 68 consecutive PTS with recurrent VF and VTS, of these 58 were male and 10 female, mean age 51.7 years. Forty-two PTS (61.7%) had documented IHD; while 8 (11.7%) had structurally normal hearts. The following table represents exposure of paroxysms of ventricular tachycardia (VT) by these two methods:

Group	Monitor	Exercise	PTS
1	+	+	27 (39.7%)
2	+	-	27 (39.7%)
3	-	+	7 (10.3%)
4	-	-	7 (10.3%)

No clinical characteristics or differing exercise hemodynamic responses distinguished these groups. Hence a substantial subset of patients with VF and VTS will demonstrate no advanced grades of VPBs during monitoring and in 10% exercise stress testing will alone disclose VT and thus assist in the management of these high risk PTS.

LIMITATIONS OF CONTINUOUS AMBULATORY ECG MONITORING FOR DETECTING CORONARY ARTERY DISEASE IN PATIENTS WITH CHEST PAIN AND NORMAL RESTING ECGS. Charles Boucher, MD; Michael Crawford, MD, FACC; David White, MD; Carlos Mendoza, MD, and Robert O'Rourke, MD, FACC, University of Texas Health Science Center, San Antonio

Continuous ambulatory ECG monitoring (CM) can detect ST segment changes in patients (pts) with significant coronary artery disease (CAD); however, many of the pts in previous studies had prior myocardial infarction or abnormal resting ECGs. To assess the reliability of CM for indicating the presence or absence of CAD in normotensive pts with chest pain and normal resting ECGs, we studied 70 such pts (55 males & 15 females) prospectively with 24 hour calibrated CM, Bruce protocol treadmill testing (TT), and selective coronary cineangiography. Positive (+) CM and TT tests were defined as ≥ 0.1 mV ST segment depression $\geq .08$ sec. Significant CAD ($\geq 50\%$ narrowing in 1 or more major vessels) was present in 39 of the 70 pts. CM was + in 36 pts, 24 of whom had CAD. CM was negative (-) in 34 pts, 15 of whom had CAD. Thus, the number of CAD pts having a +CM (sensitivity) was 24/39 (62%) and the number of nonCAD pts having a -CM (specificity) was 19/31 (61%). False +CM results occurred equally (8/21 vs 4/10) in males and females. Among the CAD pts, % maximum predicted heart rate (HR) achieved during CM was greater in those with true +CM than in pts with false -CM (67±12% vs 54±9%, $p < .01$). •Of 16 pts with main left or 3 vessel CAD, CM was + in only 9, while TT was + in all 16. Overall, the addition of TT results to CM increased the sensitivity to 33/39 (85%) but lowered the specificity to 16/31 (52%). We conclude: (1) CM alone is unreliable for detecting or excluding CAD in symptomatic patients with normal resting ECGs, (2) False -CM results are partly due to lower HRs, and (3) combining CM and TT increases sensitivity at the expense of specificity.

THE REPETITIVE VENTRICULAR RESPONSE IN MAN: AN INDEX OF VENTRICULAR ELECTRICAL INSTABILITY
H. Leon Greene, M. D.; Philip R. Reid, M. D.; Allen H. Schaeffer, M. D., The Johns Hopkins University, Baltimore, Md.

Premature ventricular stimuli (PVS) were used to assess ventricular electrical instability in 43 patients (pts) with a recent myocardial infarction (< 2 weeks), in 32 pts with recurrent ventricular tachycardia (VT), and in 10 normal controls. During atrial pacing at 700 msec, a single 0.9 msec right ventricular stimulus, < 4.0 mA, was delivered every eighth beat at 20 msec intervals from the QRS progressively back to the preceeding T wave until ventricular refractoriness was reached. Repetitive ventricular responses (RVR) were defined as multiple ventricular premature beats (≥ 2) in response to a single stimulus. All pts were followed prospectively for 1 year to assess the frequency of symptomatic VT or sudden death (SD).

None of the 10 control pts had RVR, while 27 of the 32 pts with recurrent VT had RVR ($p < 0.001$). In the 43 pts post-myocardial infarction, 15 had RVR of whom 11 pts had either symptomatic VT or SD. Conversely, only 3 of 28 survivors of myocardial infarction with no RVR developed symptomatic VT or SD ($p < 0.01$). Three of 85 pts required cardioversion for sustained VT during PVS, each of whom had had a history of recurrent VT.

Thus, the RVR identifies pts who have ventricular instability which may subsequently lead to symptomatic VT or SD in pts with ischemic heart disease.

VENTRICULAR TACHYCARDIA IN THE POSTHOSPITAL PHASE OF MYOCARDIAL INFARCTION

Kelley Anderson, M.D., John DeCamilla, B.S., and Arthur J. Moss, M.D., F.A.C.C., University of Rochester Medical Center, Rochester, New York.

The clinical significance of ventricular tachycardia (VT) recorded during ambulatory monitoring in postcoronary patients was determined from an ongoing prospective study. Six-hour Holter ECG recordings were performed every four months during follow-up periods (4-48 mo) in 915 patients <66 years of age who survived the hospital phase of myocardial infarction. Over 5000 ECG recordings in this population revealed 199 episodes of VT in 66 patients. Most patients (74%) had only one episode of VT, and in 47% of the patients the longest run of VT consisted of 3 ventricular premature beats in a row. A double set of control patients (n=132) was assembled by matching each VT patient according to sex, admission date and VT recording date. The VT and control patients were similar in almost all clinical characteristics. However, VT patients had more rapid heart rates and more evidence of ventricular irritability ($p<0.01$) than their matched controls. The mortality rate was 16% (11/66) in the VT group and 8% (11/132) in the control group ($p=0.056$). The risk ratio was 2.35 (95% confidence interval 0.82 to 6.77). Life table analysis of the survival of VT and control patients revealed a 48 mo VT survival of 75% compared to 87% in the control group. Among those who died, the age, sex, cause of death, suddenness of death and mechanism of death were similar in the VT and control patients. Within the VT group, those who died had more severe underlying heart disease than the survivors. The findings suggest that VT in the posthospital phase of myocardial infarction has less ominous implications than previously assumed.

LIMITATIONS OF INFREQUENT HOLTER MONITORING IN ASSESSING ANTIARRHYTHMIC EFFICACY

Joel Morganroth, MD, FACC; Leonard N. Horowitz, MD; Mark E. Josephson, MD, FACC; Eric L. Michelson, MD, University of Pennsylvania, Philadelphia, Pa.

Variations in frequency of ventricular (VPD) and atrial (APD) premature depolarizations were evaluated by three consecutive 24 hr Holter (H) recordings using the Avionics 2-channel 445 recorder and 660A scanner at 120X real time (with a 7% error rate compared to real time analysis). 15 patients (pts)(mean age 56 ± 10 yrs) with various cardiac disorders with VPD frequency of 37-1,379/hr underwent 20 study periods, and 8 pts (58 ± 12 yrs) with APD frequency of 63-694/hr underwent 9 study periods. VPDs varied from +578 to -73% and APDs -96 to +748% over 3 days. Mean ectopic frequencies were subjected to a 4 and 5 factor nested analysis of variance to determine the source of variation. 50% of the VPD variation was due to differences between hourly rates whereas the largest APD variation was due to day to day variations. For significant change in ectopic frequency to exceed spontaneous variation, the following % decrement in ectopic frequency (depending on the protocol used) is necessary:

	Control (H)	Post-Intervention (H)	VPDs	APDs
Protocol Design:	One: 8 hr	One: 8 hr	-90%	-99%
	One: 24 hr	One: 24 hr	-83%	-98%
	Three: 24 hr	Seven: 24 hr	-58%	-85%
	Seven: 24 hr	Seven: 24 hr	-49%	-78%

Thus, to determine the efficacy of an antiarrhythmic agent using specific research or clinical protocols, the decrease in ectopic frequency must exceed the values given in the table before that change in frequency can be considered statistically significant.

EVIDENCE FOR DOMINANCE OF THE LEFT STELLATE GANGLION IN THE LONG Q-T SYNDROME

Richard S. Crampton, MD, FACC, 158 Medical Center, University of Virginia, Charlottesville, Virginia 22901.

The influence of left (L) and right (R) stellate ganglion block (SGB) and stimulation (S) and drug treatment upon Q-Tc (Bazett), Q-T and T alternans (ALT) and ventricular ectopy (VE) was assessed in 6 patients with Romano-Ward syndrome with Q-Tc mean (range) .61(.52-.71) sec. Five had ventricular tachycardia and 4 fibrillation. For SGB with lidocaine and for SGS (technic of GM Vincent et al, Am J Cardiol 33:174, 1974) with 1.5 msec rectangular DC pulses (9-10 Hz, 0.5-30V), the Q-Tc of 10 consecutive sinus beats before, during and after intervention was compared (t test) for directional change (Table). P ranged from <.0001 to <.05 for significant decrease (↓) or increase (↑) and >.6 for no change (→). The 12 lead ECG (3 simultaneous) was recorded at 50 mm/sec, 0.5 mV/cm.

	LSGB	RSGB	LSGS	RSGS
Q-Tc	↓4, ↑1	↑4	↑2, →1	↓2, ↑1
Q-T&T ALTERNANS	↓2	↑2	↑2	→
V ECTOPY	↓2	↑1	↑1	→

Propranolol and phenytoin, alone or together, abolished ALT in 5 of 6 and KCL and Mg SO4 in 1 of 1. These agents and bretylium suppressed VE. Procainamide and quinidine worsened ALT and VE in 2 of 2. In summary, the shortening of Q-Tc and suppression of ALT and VE by LSG block and by antisympathetic drugs and the elongation of Q-Tc and production of ALT and VE by LSG stimulation and RSG block militate for asymmetric cardiac innervation with LSG dominance as the major cause of syncope, VE and sudden death in long Q-T syndrome. Moreover, the rationale (PJ Schwartz et al, Am J Cardiol 37:1034, 1976) for excision of the LSG for refractory ventricular tachydysrhythmias in the long Q-T syndrome is supported by these observations.

DOES CORONARY REVASCULARIZATION REDUCE THE PREVALENCE OF VENTRICULAR ECTOPIC ACTIVITY?

Thomas B. Graboys, MD; Bernard Lown, MD, FACC; John J. Collins, MD, FACC; Lawrence H. Cohn, MD, FACC, Harvard School of Public Health and Peter Bent Brigham Hospital, Boston, Mass.

If ventricular ectopic activity (VEA) in patients with coronary heart disease relates to myocardial ischemia, then improved vascularization should reduce the prevalence of arrhythmia. This question was examined in 58 patients (PTS)(50 male, 8 female; mean age 51, range 25-74) who were subjected to 24 hour ambulatory monitoring (MON) two days before and at least one week after coronary bypass graft surgery (CABG). Twenty-eight of these PTS underwent a third MON at 3 months post CABG. VEA was classified as follows: Grade 1 (≤ 1 VPB/min); Grade 2 (≥ 30 VPBs/hr); Grade 3 (multiform); Grade 4 (couplets, 4A or ventricular tachycardia, VT, 4B). Detailed below are the results of monitoring at 1 week (MON 2) and at 3 months (MON 3) as compared to pre-CABG MON:

	VEA		
	Increased	Decreased (%)	No Effect
MON 2	28 (48.2)	9 (15.5)	21 (36.2)
MON 3	14 (50)	4 (14.3)	10 (35.7)

Eleven (39.2%) of the 28 PTS monitored at 3 months demonstrated advanced grades (4A,4B) of VEA, 5 of whom first developed VT post CABG persisting during MON 3. Nine of the 28 PTS monitored at 3 months who had been free of VEA prior to CABG persistently demonstrated VEA post CABG. Among 37 of 58 PTS (63.7%) in the immediate post CABG period and 18 of 28 PTS (64.2%) monitored at 3 months the same or an increased grade of VEA could be demonstrated. Hence coronary revascularization does not have a salutary effect upon VEA.

MODE OF DEATH DURING LONG-TERM FOLLOW-UP OF CORONARY ARTERY BYPASS PATIENTS.

Haydi Guild, Barbara Blake, R.N., John A. Murray, M.D., F.A.C.C., Seattle Heart Watch, University of Washington, Seattle, Washington.

To assess the pattern of mortality following coronary artery bypass grafting (CABG), death certificates, autopsies, survivor interviews and hospital records were reviewed in 123 (7.2%) mortalities which occurred in 1714 hospital survivors of CABG followed for an average of 46± 17 months. Eighty-four (4.9%) patients were lost to follow-up.

Four modes of death, based upon the duration of final episodes were determined:

INSTANTANEOUS CARDIAC DEATH, (final event, 0-60 minutes), 55 patients (45%).

SUDDEN CARDIAC DEATH, (final event 1-24 hours), 11 patients (9%).

NON-SUDDEN CARDIAC DEATH, (final event more than 24 hours), 21 patients (17%).

NON-CARDIAC DEATH, 36 patients (29%).

Cancer caused 16 of the 36 non-cardiac deaths for an annual rate of 2.7/1000 man years.

Death occurred within 24 hours in 66 (54%) patients, of these, 49 (74%) died outside of hospital of presumed ventricular fibrillation.

Unexpected, out of hospital cardiac mortality is the most frequent final event for patients following treatment by CABG. Mechanisms of these events is unexplained but attention to arrhythmia control and family training in cardiopulmonary resuscitation is suggested.

WEDNESDAY, MARCH 8, 1978
AM
HYPERTENSION
8:30 to 10:00

SEX AND RACE DIFFERENCES IN END ORGAN DAMAGE AMONG 10,940 HYPERTENSIVES

The HDFP Cooperative Group presented by Ronald Prineas, M.B.,Ph.D., on behalf of the HDFP Cooperative Group. University of Minnesota, Minneapolis, Minnesota.

This report describes age, race and sex-specific differences in cardiac injury accompanying moderate hypertension in the general population. The prevalence of end-organ damage among hypertensives has been examined by coding ECG criteria for 10,940 hypertensive men and women. These persons (aged 30-69 years) are participants in a population based study - the Hypertension Detection and Follow-up Program (HDFP). At baseline examination in 1973-74, standard 12 lead, 3 channel ECGs were recorded in a fasting state using a standard protocol. All ECGs were masked and triple-read, centrally. Positive associations between levels of blood pressure (BP) and maximal voltage in limb and chest leads were observed. ECG evidence of left ventricular hypertrophy was more prevalent in men than women and in blacks than whites, after adjusting for age and BP level. The most common ECG abnormalities present were T-wave and ST-segment changes. The most common Q-wave abnormality was a Q-wave in excess of 5 mm in lead III. Among the mild hypertensives, with diastolic BP 90 to 104 mm Hg, 22.1% had a major ECG abnormality; 12.6% had excessively tall R waves and 3.5% had tall R waves associated with ST and T-wave abnormalities. Thus, a sizeable proportion of hypertensive people in the general population meet present criteria for instituting antihypertensive treatment.

EVALUATION OF DIZZINESS AND SYNCOPE BY 24-HOUR AMBULATORY ELECTROCARDIOGRAPHY.

Harold L. Kennedy, MD, MPH, FACC; Carol J. Wheeler, Pio F. Poblete, MD; and Dennis G. Caralis, MD, Department of Cardiovascular Services and Clinical Investigations, U.S. Public Health Service Hospital, Baltimore, Maryland.

To determine the usefulness of 24-hour ambulatory electrocardiographic recordings (HR) in the evaluation of patients with symptoms of lightheadiness or dizziness (D) and syncope (S), 1957 24-hour HR were reviewed. A history of D (30 patients) or S (102 patients) with unknown etiology was the indication for HR in 132 patients and defined the study group.

In the study group, 31 patients (23 percent) complained of D during HR (S did not occur) which correlated with causal ECG dysrhythmias in 9 patients (7 percent). Causal dysrhythmias found included Mobitz II AV block with profound sinus bradycardia in 2, supraventricular tachycardia in 4, slow sinus bradycardia in 1, and ventricular tachycardia in 2 patients. Of 22 patients (17 percent) with symptoms which did not correlate with causal dysrhythmias, 10 had normal ECG findings and 12 had arrhythmias (4 supraventricular, 4 ventricular, and 4 both). Of the 101 patients (77 percent) who experienced no symptoms during the 24-hour HR, 5 patients (4 percent) showed dysrhythmias suspected of a potential symptom-provoking nature. These dysrhythmias consisted of intermittent bundle branch block in 3, intermittent Mobitz I AV block in 1, and sinus node disease in 1 patient. The remaining 96 patients were found to have normal ECG findings in 30 (23 percent) and minor arrhythmias in 66 (50 percent).

In this study evaluating 132 patients with D or S by 24 hour HR:

a) 23 percent (31 of 132) of patients had symptoms during the 24-hour HR evaluation.
b) 11 percent (14 of 132) of patients had either symptoms correlated with causal ECG abnormalities (9) or asymptomatic major ECG abnormalities probably causal of symptoms (5).
c) Regardless of the presence or absence of symptoms during HR, most patients (89 percent) had normal 24-hour HR (30 percent) or minor ECG arrhythmias (59 percent) which did not correlate or seem related to D or S.
d) The necessity for specific careful clinical correlation of symptoms and ECG abnormalities to avoid misinterpretation and unnecessary therapy is evident.

HEMODYNAMICS OF ORALLY-ACTIVE CONVERTING ENZYME INHIBITOR (SQ14225) IN HYPERTENSIVE PATIENTS

Robert J. Cody, Jr., MD; Robert C. Tarazi, MD, FACC; Emmanuel L. Bravo, MD; Fetnat M. Fouad, MD, The Cleveland Clinic Foundation, Cleveland, Ohio

Hemodynamic response to SQ14225 was investigated in 8 patients with severe essential or renovascular hypertension, on 100 mEq/day sodium intake. Data were obtained over 2-3 weeks, during control, maintenance and withdrawal stages. Mean arterial pressure (MAP) was reduced by > 10 mmHg in 6/8 pts. (147 ± 7 to 118 ± 9, $p < 0.0025$) due to decreased total peripheral resistance (TPR) (55 ± 5 to 42 ± 4 units, $p < 0.01$), with minimal increase in cardiac index (CI) (2.78 ± 0.18 to 2.90 ± 0.19 L/min/M^2, $p < 0.05$). Heart rate response was variable (range +8 to -9). The two non-responders had no substantial change in hemodynamic indices.

In 4/8 pts. (1 non-responder and 3 partial responders), addition of low salt diet (10 mEq/day) further reduced MAP (137 ± 8 to 111 ± 12, $p < 0.025$) through decreased TPR (49 ± 4 to 39 ± 3, $p < 0.025$) with no change in CI (2.82 ± 0.05 to 2.79 ± 0.12, NS) and variable plasma volume (PV) response (range +0.8 to -1.5 ml/cm). Regardless of sodium intake, MAP and TPR returned toward control levels with SQ14225 withdrawal. Baroreceptor response was unaltered by drug therapy [increased HR (32 ± 6) and TPR (17 ± 2) on tilt to 75°], in 6/6 pts. tested.

In summary, SQ14225 blood pressure reduction occurred through decreased TPR without CI or HR diminution; this could be augmented by low sodium diet. SQ14225 did not alter the baroreceptor response, yet on maintenance therapy, decreased TPR did not induce the magnitude of HR and CI increase seen with vasodilators.

PRELOAD AND AFTERLOAD REDUCTION DURING ANGIOTENSIN II BLOCKADE WITH THE CONVERTING ENZYME INHIBITOR.

A.P. Niarchos, MD, T.G. Pickering, MD, D.B. Case, MD, J.M. Wallace, MD, A. Morganti, MD, J.E. Sealey, DSc, and J.H. Laragh, MD, FACC. Cardiovascular Center, The New York Hospital-Cornell Medical Center, New York, N.Y. 10021

The hemodynamic effects of the converting enzyme inhibitor (CEI, SQ20881) were investigated in 7 normotensive patients (group I) with normal plasma renin activity (PRA), in 5 hypertensives with normal PRA (group II), and in 5 hypertensives with high PRA (group III). No significant hemodynamic changes were observed during CEI administration in group I. In group II a 16% decrease ($p<.05$) was observed in stroke index (SI), and cardiac index (CI) which resulted in a 12% decrease ($p<.0005$) in mean arterial pressure (MAP), but without change in total peripheral resistance (TPR). In group III the 19% decrease in MAP ($p<.0005$) was due to a significant fall in TPR (by 30%, $p<.005$); in this group SI and CI were significantly increased (by 14%, $p<.05$). There were no compensatory changes in heart rate (HR) neither in group II nor in group III. These results indicate that: 1) in hypertensive patients with high PRA, CEI decreases MAP by decreasing TPR; in this group SI and CI are increased; 2) in hypertensives with normal PRA, CEI decreases MAP by reducing CI, an effect which is the result either of venodilatation or decreased myocardial contractility; 3) acute angiotensin II blockade concurrently modulates baroreceptor mediated responses in HR as evidenced by the lack of expected increase in HR during hypotension.

EFFECTS OF ANTIHYPERTENSIVE THERAPY (AHT) ON CARDIOVASCULAR RESPONSES TO EXERCISE

Won Ro Lee, MD; Lay M. Fox, MD, FACC; Lawrence M. Slotkoff, MD, Georgetown University and District of Columbia General Hospital, Washington, D.C.

The effects of AHT on exercise induced changes in heart rate (HR), systolic pressure (SP), diastolic pressure (DP), and rate pressure product (RPP), an index to total tension generated, were evaluated by graded treadmill exercise (TM) to subjective maximal tolerance (SM) in 15 mild to moderate hypertensive patients (12 males and 3 females) before (C) and during AHT. Both hydrochlorothiazide (HCTZ) and alpha methyl dopa (AMD) were used for AHT individually for 4 weeks given in random fashion. Each subject served as his own control. Neither HCTZ nor AMD changed HR response to TM. Both HCTZ and AMD reduced resting SP and DP to comparable levels (SP: C 155 mmHg; HCTZ 134, $p<0.001$; AMD 130, $p<0.001$. DP: C 104; HCTZ 93, $p<0.001$; AMD 90, $p<0.001$). There was no change in BP response to TM or to recovery during HCTZ. AMD, however, reduced SP and DP at the initial stage (SP: C 194; AMD 173, $p<0.01$. DP: C 108; AMD 102, $p<0.01$) and at SM (SP: C 218; AMD 200, $p<0.05$. DP: C 111; AMD 102, $p<0.05$). SP and DP were significantly less compared with C at all levels of early recovery phase of TM during AMD (Post-TM 1 min: SP C 189, AMD 165, $p<0.01$; DP C 101, AMD 92, $p<0.05$. Post-TM 3 min: SP C 160, AMD 140, $p<0.001$; DP C 104, AMD 93, $p<0.01$. Post-TM 5 min: SP C 150, AMD 131, $p<0.001$; DP C 103, AMD 89, $p<0.001$). RPP was significantly reduced by AMD. Neither HCTZ nor AMD changed the total duration of TM tolerance. Whereas HCTZ failed AMD significantly reduced pressure response i.e. tension generated during exercise presumably reducing myocardial oxygen demand without reducing work capacity.

THE INTERACTION BETWEEN SYMPATHETIC NERVOUS SYSTEM, RENIN-ANGIOTENSIN AND SODIUM BALANCE IN BLOOD PRESSURE MAINTENANCE DURING TILT IN ESSENTIAL HYPERTENSIVE PATIENTS.

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The effect of a 30 min 65° head up tilt on BP, HR and plasma renin activity (PRA) was evaluated in 7 essential hypertensive patients (EHT) on 100 mEq sodium diet before and after 0.12 mg/kg propranolol i.v.
Before propranolol mean BP was unchanged during tilt while HR increased by 23.5 ± 1.7 beats/min and PRA by 2.9 ± 0.9 ng/ml/h. During propranolol 3 patients fainted after a mean of 20 min tilt. In those who did not faint BP fell by 18.0 ± 10.6 mmHg and HR increased by only 9.5 ± 4.2 beats/min, that is a 63% ± 16 blockade of the HR response. The PRA increase was abolished by propranolol in all but the one patient who had the highest pretreatment PRA increase (6.7 ng/ml/h) and the least effective blockade of the HR response during tilt (19%).
In 4 of the patients studies were repeated after sodium deprivation and sodium loading. On both diets before propranolol mean BP was again unchanged during tilt, HR had similar increases (28.7 ± 9.3 vs. 28.0 ± 8.7 beats/min) while PRA always increased more after sodium deprivation (mean 3.4 ± 2.3 vs. 1.2 ± 0.5 ng/ml/h). After propranolol all sodium depleted patients developed hypotension and fainted whereas BP decreased in only 2 after sodium loading (mean 8.6 ± 4.4 mmHg); HR increases were similarly blunted (57% ± 10 vs. 51% ± 11 blockade) and PRA increases were again abolished. These data show that PRA increases during tilt in EHT are mainly ß-adrenergically mediated and suggest that the renin-angiotensin system is an adjunctive pathway supporting BP during tilt. This support is inversely related to the state of sodium balance.

ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR RESPONSE TO EXTREMES OF SALT INTAKE IN NORMO-TENSIVE MAN

Arthur E. Weyman, M.D., F.A.C.C., Friedrich C. Luft,M.D., Richard Bloch, M.D., Raymond H. Murray, M.D., Myron Weinberger, M.D., Jane Marshall, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Left ventricular performance in response to extremes of salt intake was evaluated echocardiographically in 8 normal men (ages 29 to 40). In addition to their normal diet patients were given 4 levels of daily sodium intake as follows: 10 mEq x 7 days; 300 mEq x 3 days; 800 mEq x 3 days; 1500 mEq (800po, 700 iv) x 3d. K+ intake was 75 mEq/day. Parameters studied included end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV), cardiac output (CO), heart rate (HR), urinary sodium excretion ($U_{Na}V$) and mean arterial blood pressure (MABP).
Results (mean ± SD) are:

Na+ intake (mEq/d)	10	300	800	1500
EDV - cc	125±16	136±18	142±19	153±15
ESV - cc	39±7	44±6	39±7	35±7
SV - cc/Beat	86±12	93±13	100±11	115±10
CO L/min	5.3±0.5	5.9±1.2	5.8±1	6.9±1.8
HR Beats/min	62±15	63±13	58±9	60±15
$U_{Na}V$ (mEq/d)	12±4	265±68	702±62	1442±100
MABP (mmHg)	83±6	84±7	90±8	99±9

With increasing levels of salt intake significant increases in EDV ($P = <.001$) SV ($P = <.001$) and CO ($P = <.025$) were observed. HR and ESV did not change significantly. Both SV and CO correlated with urinary NA excretion $r = 0.58$, $P < .001$, and $r = 0.42$, $P < 0.02$. Since the observed changes in MABP cannot be explained by an increase in systemic vascular resistance these data suggest that increased MABP at increasing salt loads is due to the observed increase in CO and SV.

WEDNESDAY, MARCH 8, 1978
AM
CARDIOVASCULAR EPIDEMIOLOGY
10:30 to 12:00

THE COMBINED EFFECT OF SMOKING AND COFFEE DRINKING ON LDL-HDL CHOLESTEROL

Curtis Hames, M.D., FACC; Siegfried Heyden, M.D.; Herman Tyroler, M.D.; Gerardo Heiss, M.D.; Gerald Cooper, M.D.; Christian Manegold, M.D., Evans County Heart Research, Claxton, Ga.

Several prospective studies have recently reported on the influence of either caffeine or smoking on HDL and LDL cholesterol. To clarify prevailing inconsistencies, the combined effects of coffee drinking and smoking on HDL and LDL were studied in a random sample of the Evans Co. cohort (n=398) as part of the National Lipoprotein Phenotyping Study. Results: In each subgroup, i.e. blacks, whites, males, females, a consistent trend of increasing LDL and decreasing HDL levels with the number of cigarettes smoked was noted. Lowest LDL and highest HDL levels in non-smokers (N.S.) and the reverse finding in heavy smokers, however, were only demonstrated in the high coffee users (>5 cups/day). Among low-or no coffee drinkers no relationship between cigarette smoking and any of the lipid parameters mentioned was discernable. Whereas low coffee consumers displayed LDL levels of 130 mg/dl in N.S., 130 mg/dl in <15 cigarettes/day smokers and 132 mg/dl in those smoking >15 cigarettes, the high coffee users showed levels of 130, 146, 152 mg/dl, respectively. Similarly, HDL among low coffee consumers varied from 57 to 62 to 54 mg/dl, but in the high coffee drinking group decreased from 64 to 52 to 45 mg/dl, respectively, in the three smoking categories. Neither heavy cigarette smoking alone nor a habitual high coffee usage per se seems to produce undesirable lipoprotein changes. However, results of this study which were adjusted for age, weight (Quetelet Index), race and sex, indicate the presence of an interactive effect of heavy smoking and high coffee use on lipids and lipoproteins.

DECREASE IN PLASMA HIGH DENSITY LIPOPROTEIN CHOLESTEROL CONCENTRATION WITH WEIGHT LOSS

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Although epidemiological studies show that high-density lipoprotein cholesterol (HDL-CHOL) plasma concentration is inversely related to relative body weight, few prospective studies on the effects of weight loss on HDL-CHOL have been done. Plasma lipoproteins were measured by indirect beta quantification in 15 obese females (mean weight = 100.3±22.5 kg) before and after a ten-week treatment program based on calorie intake reduction. Mean weight loss was 8.6±3.9 kg (p<0.001). Total cholesterol (T-CHOL) and low-density lipoprotein cholesterol (LDL-CHOL) did not change significantly. Triglycerides (TG) and HDL-CHOL decreased significantly. There was no correlation between weight lost and lipoprotein concentration change. No change in alcohol intake or physical activity was detected by comparing pre- and post-treatment questionnaires.

	TG	T-CHOL	HDL-CHOL	LDL-CHOL
Initial Value	128.3±64.9	209.9±36.3	50.8±11.8	133.5±35.2
Change	-17.8±31.4	-9.0±22.8	-3.8± 5.0	-1.6±17.8
p	<0.05	NS	<0.02	NS

The unexpected decrease in HDL-cholesterol with weight loss suggests that the observed inverse correlation between relative weight and HDL-cholesterol may be due to factors, such as decreased physical activity, associated with obesity rather than to obesity itself.

COMPARISON OF SERUM CONCENTRATION OF HIGH DENSITY LIPOPROTEINS IN NORMALS AND PATIENTS WITH CORONARY ARTERY DISEASE: IMPORTANCE OF THIS LIPOPROTEIN FRACTION AS AN INDEPENDENT RISK FACTOR IN FEMALES

Harbhajan S. Sodhi, MD; Anthony N. DeMaria, MD, FACC; James E. Price, MD; Robert D. Swenson, BS; Jess F. Kraus, PhD; Carolyn Clifford, PhD; Nemat O. Borhani, MD, FACC; Thomas R. Fashinell, MD; Dean T. Mason, MD, FACC, University of California, Davis, California

To determine whether high density serum lipoprotein cholesterol (HDL; mg/dl) is an independent risk factor in coronary disease (CAD), fasting lipid levels were analyzed in 102 Caucasian patients (pts) undergoing coronary angiography: 66 with CAD and 36 normals (NL).

	Cholesterol	Triglycerides	HDL	VLDL	LDL
CAD	246.5*	173.6	32.2*	49.2	**161.2
NL	205.6	115.3	41.5	28.9	136.5

*p<.01 CAD vs NL; **p<.05 CAD vs NL; VLDL = very low density serum lipoprotein cholesterol (mg/dl); LDL = low density serum lipoprotein cholesterol (mg/dl); cholesterol and triglycerides (mg/dl). The prevalence of other coronary risk factors including hypertension, smoking, obesity, glucose intolerance and CAD family history were similar in NL and CAD. When subjected to stepwise discriminate analysis (SDA), the above data showed HDL to be the single most important factor (p<.01) in discriminating CAD from NL. However, since HDL was significantly correlated with sex (R = .264, p<.01), sex specific SDA was repeated. Results showed most important coronary risk factors in males were CAD family history and obesity. However, in females HDL was the most important coronary risk factor which was independent of other variables. Thus, in evaluation of SDA risk factors, it is important to analyze HDL cholesterol as well as LDL cholesterol, especially in the female population.

EFFECT OF PARTIAL ILEAL BYPASS ON PLASMA LIPOPROTEINS

Richard B. Moore, MD, FACC, Richard L. Varco, MD, and Henry Buchwald, MD, FACC, University of Minnesota, Minneapolis, Minnesota.

Partial ileal bypass (PIB) in the most effective means of reducing plasma lipid levels. Plasma cholesterol (C), triglycerides (TG), and lipoprotein (LDL,VLDL,HDL) cholesterol (mg/dl) were measured in 53 (48 M, 5 F) coronary heart disease (prior MI) subjects aged 30-60yrs. HDL-C was measured after heparin-$MnCl_2$ precipitation of LDL & VLDL; plasma was ultracentrifuged (d.1.006, 18 hr, 40,000 rpm and bottom (HDL+LDL)-C measured; LDL-C= (bottom-C) - HDL-C; VLDL-C= (plasma-C) - bottom-C. PIB was done in 23 M & 5 F and the study repeated after 3 months. The results are listed below: (Italics=3 mo after PIB; n in ( )).

	Normal(8)	II-A(6)	II-B*	IV (5)	V*
C	237.3±13	380.0±39	306	263.8±21	355
	158.9±19	*188.7±45*	*178*	*166.4±22*	*197*
TG	125.6±32	160.8±39	223	380.2±155	1717
	161.5±37	*163.7±78*	*246*	*244.2±40*	*938*
LDL	171.8±14	243.7±36	219	155.8±42	78
	80.5±12	*124.7±45*	*92*	*90.0±23*	*66*
VLDL	18.6±5	24.5±10	45	65.2±28	229
	23.8±9	*26.5±16*	*35*	*32.8±13*	*80*
HDL	49.4±10	41.3±7	50	40.8±5	31

All LP types showed marked and significant (p<.001) reductions in plasma cholesterol and LDL-C; types II-B, IV, and V had marked reductions in plasma triglycerides and in VLDL-C; there were no significant changes in HDL-C.In 7 subjects restudied 1 yr after PIB these changes were maintained. We conclude that PIB effects marked and permanent reductions in the elevated plasma lipids and lipoproteins present in the hyperlipoproteinemias. This action results in a normalization of the plasma lipoproteins.

(*n = 2 in each group)

RESULTS OF A CONTROLLED INTERVENTION TRIAL ON VENTRICULAR DYSRHYTHMIAS

Guy DeBacker, MD, FACC; David Jacobs, PhD; Ronald Prineas MBBS, PhD, FACC; Richard Crow, MD; Harold Kennedy, MD; Henry Blackburn, MD, FACC; Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota Minneapolis, Minnesota.

Using a randomized controlled and partial cross-over design, the influence was tested of six weeks intervention on factors related to myocardial excitability. The regimen included total abstinence from caffeine and smoking together with reduction of alcohol intake and a physical conditioning program. Effects were studied in 89 men having persistently measurable ventricular dysrhythmias. Ventricular premature beats (VPB) were measured in standardized rest, dynamic and isometric exercise tests, and in 24-hour ambulatory monitoring. Compliance was excellent in that 83% of smokers quit entirely, and more than 90% abstained from caffeine, limited alcohol intake and attended the exercise training sessions. VPB rates were analyzed as VPB/min., log normal VPB/min. and VPB/100 beats. Modest changes occurred in both experimental and control groups, but no significant group differences appeared in VPB rates at rest or during any of the induction tests. The six week multiple factor intervention program had no significant influence on VPB activity measured under various conditions in apparently normal men having frequent VPB. Because of their different mechanisms and significance, the potential for "hygienic" VPB suppression should also be studied in coronary patients.

WEDNESDAY, MARCH 8, 1978
AM
ECHOCARDIOGRAPHY—I
10:30 to 12:00

ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR PERFORMANCE DURING SUPINE AND UPRIGHT BICYCLE EXERCISE.

Michael Crawford, MD, FACC and Wray Amon, University of Texas Health Science Center, San Antonio, Texas

The echocardiographic evaluation of left ventricular (LV) performance may become more sensitive if measurements are made during exercise as well as at rest. Therefore, we measured LV end-diastolic dimension (Dd), end-systolic dimension (Ds) and the percent of dimension shortening (%ΔD=Dd-Ds/Ddx100%) in 10 normal subjects during 9 or more minutes of graded supine and upright bicycle exercise. Echocardiography during upright exercise was accomplished by a hand held transducer utilizing an adjustable platform to stabilize the subject and the echocardiographer. The mean values for heart rate (HR), systolic blood pressure (SBP), Dd, Ds and %ΔD in our 10 subjects during both forms of exercise are as follows:

	SUPINE		UPRIGHT	
	Rest	Exercise	Rest	Exercise
HR bpm	66±4(SE)	120±4*	72±5	123±7*
SBP mmHg	109±2	151±4*	106±3	140±4*
Dd mm	51±1	52±1	47±1	49±2
Ds mm	32±1	27±1*	30±1	25±1*
%ΔD	37±2	48±1*	37±2	50±2*

* = $p < 0.001$ as compared to the resting value

These data indicate that LV end-diastolic size is maintained during moderate dynamic exercise even in the upright position and that there is an increase in LV shortening during exercise. Both findings are consistent with previous invasive studies in animals and in man. We conclude that echocardiographic measurements of LV performance can be made in normal subjects during moderate supine and upright bicycle exercise. Furthermore, this noninvasive procedure may be useful for studying interventions that affect LV performance only during exercise.

DETERMINANTS OF RISK OF SUDDEN HIGH DEGREE A-V BLOCK DURING MYOCARDIAL INFARCTION WITH BUNDLE BRANCH BLOCK

Michael Hindman, M.D., Marlene Jaro, James Morris, M.D., Lawrence Yeatman, M.D., Melvin Scheinman, M.D., James Atkins, M.D., Melvin Rubenfire, M.D., Galen S. Wagner, M.D. Duke Hosp., Durham, N.C., Mass. Gen. Hosp., Boston, Mass., S.F. Gen. Hosp., S.F., Calif., Parkland Mem. Hosp., Dallas, Texas.; Sinai Hosp., Detroit, Mich.

Indication for prophylactic temporary pacemaker (PTP) insertion in myocardial infarction (MI) complicated by bundle branch block (BBB) is high risk of progression to Type II or 3rd° block (Hi°AVB). This study includes 494 patients (pts) from five medical centers with MI and left (LBBB), right (RBBB), RBBB+left anterior (LAH) or left posterior (LPH) blocks, or alternating RBBB+LBBB. The involved fascicles, timing of onset of BBB, and PR interval were examined as determinants of risk of Hi°AVB. Low (9-11%, intermediate (19-20%), and high (29-38%) risk groups were identified depending upon (1) combination of RBBB with LAH, LPH or LBBB (combo), (2) BBB not previously observed before MI (new) and (3) first degree A-V block (1°AVB). At lowest risk were 168 pts with none or only one of the three determinants. At intermediate risk were 78 pts with either new LBBB or RBBB with 1°AVB or old combo blocks with 1°AVB. At highest risk were 186 pts with new combo blocks either with (38% risk) or without (29% risk) 1°AVB (high vs intermediate or low $p<.02$). Thus, observation of time of onset of BBB, QRS morphology, and PR interval assists in predicting risk of progression to Hi°AVB and provides the basis for a decision regarding prophylactic temporary pacemaker insertion.

IN VITRO AND IN VIVO EVALUATION OF PORCINE BIOPROSTHESES BY CROSS-SECTIONAL ECHOCARDIOGRAPHY

William Bommer, MD; David Yoon, BS; Todd M. Grehl, MD, FACC; Dean T. Mason, MD, FACC; Alexander Neumann, BS; Anthony N. DeMaria, MD, FACC, Univ. of California, Davis, California

To provide the basis for the clinical evaluation of the porcine bioprosthesis (PROS), two-dimensional echograms (2-D) were performed in a fluid chamber and in 15 patients (pts) with catheterization documented normal PROS function: 8 aortic (AO), 8 mitral (MV), and 1 tricuspid. Leaflet motion in vitro was related to stroke volume (SV): low flow (SV 20 cc) produced partial opening of one leaflet while intermediate flow (SV 40 cc) and high flow (SV 60 cc) completely opened all leaflets. Complete opening occurred earlier with high than intermediate flow; 30 vs 80 msec. In vivo, leaflet width on echogram always measured 3 mm or less. 2-D enabled the easy visualization of sewing ring and stents in all cases, and the measurement of ring echo by 2-D correlated with actual ring size (19-33 mm) in all cases. Two leaflets were imaged in systole in all mitral and tricuspid prostheses, but only 4 AO prostheses. Visualization was limited to one leaflet throughout diastole in 7 MV, and opening was partial (50° from closed position) in 3, (75°) in 2, and complete (90°) in only one. Leaflet opening required at least 30 msec in all cases and was characterized by an initial reversal of the curvature of the leaflet. Rocking of these normally functioning PROS was determined to be less than 10° from a line perpendicular to the sewing ring in all cases. Thus, the movement of the leaflets of a porcine bioprosthesis is related to transvalvular flow, and opening motion may be incomplete on 2-D even in the presence of normal function. 2-D enables the accurate visualization of PROS, and discerns echoes from sewing ring, stents, and leaflets. In a normally functioning PROS, leaflet width should be 3 mm or less and ring motion 10° or less by 2-D examination.

TWO-DIMENSIONAL ULTRASONIC SECTOR SCANNING FOR ASSESSMENT OF PATIENTS WITH BIOPROSTHETIC VALVES

Jay N. Schapira, MD; Randolph P. Martin, MD; Robert E. Fowles, MD; Harry Rakowski, MD; Edward B. Stinson, MD,FACC; James W. French, MD, FACC; Norman E. Shumway, MD; FACC; Richard L. Popp, MD, FACC, Divisions of Cardiology and Pediatric Cardiology, and Dept. of Cardiovascular Surgery, Stanford Medical Center, Stanford CA.

The utility of sector scanning (SS)for assessment of patients (pts) with bioprosthetic valves (BPV) was reviewed in all 40 pts referred for SS study from 3/76 to 9/77. SS was read prior to invasive procedures in all cases. Confirmation of SS findings in the 39 of 40 pts with technically adequate studies was by hemodynamics-angiography, surgery and/or pathology in 21 of 39 pts, inferred by blood cultures in 10 of 39 pts and was on clinical grounds in 8 of 39 pts. All 7 of the 39 pts considered normal clinically and referred for baseline studies had normal SS. The other 32 of 39 pts had clinically suspected cardiac dysfunction.

Sixteen of these 32 pts had abnormal BPV and normal left ventricular (LV) function by SS. Findings were confirmed in 15 of these 16 pts: 6 pts with leaflet thickening;6 pts with BPV masses; 2 pts with BPV masses and ring dehiscence; and 1 pt with leaflet dehiscence. One other BPV mass on SS was actually an area of perivalvular fibrosis at surgery.

In the remaining 16 of 32 pts with suspected cardiac dysfunction, SS findings were confirmed in: 8 pts with normal BPV and normal LV;6 pts with normal BPV and LV dysfunction; and 1 pt with abnormal BPV and LV dysfunction. The remaining pt had a normal BPV and normal LV but an interventricular septal abnormality on SS that was identified at surgery to be a sinus tract.

We conclude that SS was very useful in assessing both BPV and LV function in this series and led to a correct diagnosis in 38 of 39 pts.

TWO-DIMENSIONAL ECHO ASSESSMENT OF RESIDUAL MYOCARDIAL FUNCTION IN LEFT VENTRICULAR ANEURYSM

Michael Barrett, MD, Yzhar Charuzi, MD, FACC, Robert M. Davidson, MD, FACC, Robert Silverberg, MD, Ming K. Heng, MD, H.J.C. Swan, MD, FACC, Eliot Corday, MD, FACC, Cedars-Sinai Medical Center, Los Angeles, Calif.

Two-dimensional echocardiography was used to evaluate residual myocardial wall motion in patients with left ventricular (LV) aneurysm. A comparison was made between the sector scan findings and those made with biplane LV cineangiography (LVC).

In 10 patients with stable ischemic heart disease, echocardiographic examination using an 84° phased array sector scan (PASS) was performed by utilizing multiple transducer positions. The heart was divided into 9 segments for both PASS and LVC analysis. Segmental wall motion was graded as normal or abnormal by both techniques. The echocardiograms and cineangiograms were read indepently by 2 or more observers without knowledge of the findings of the other technique. PASS visualized 86 of 90 myocardial segments.

The localization of the aneurysm by PASS coincided with that found by cineangiography in all 10 cases. At the base, qualitative wall motion agreed in 29 of 34 segments (25 of 27 normal by LVC, 4 of 7 abnormals by LVC). At the level of the papillary muscles agreement was present in 23 of 34 segments (8 of 13 normals, 15 of 21 abnormals). The discrepancy of findings may reflect overlap of images in the left anterior oblique LV cineangiogram and/or less precise visualization of the right anterior oblique projection by PASS.

Conclusion: Thus, while the 2 techniques are complementary, the 2-dimensional echo is a noninvasive repeatable means to localize ventricular aneurysm. It also is a reliable method to assess the residual myocardial function.

FURTHER CHARACTERIZATION OF THE HYPERTROPHIC CARDIOMYOPATHY OF INFANTS OF DIABETIC MOTHERS.

Howard P. Gutgesell, MD, Michael Speer,MD, and Harvey S. Rosenberg, MD, Depts of Pediatrics and Pathology, Baylor College of Medicine, Texas Children's Hospital, Houston.

To further define the nature of hypertrophic cardiomyopathy in infants of diabetic mothers, we studied 27 infants with maternal diabetes (White class A-D). All infants had respiratory distress and eight required assisted ventilation. A systolic ejection murmur was present in seven, radiographic evidence of cardiomegaly in 13, and electrocardiographic abnormalities in 12(right ventricular hypertrophy in eight, biventricular hypertrophy in four). Echocardiography revealed hypertrophy of the septum in 12 and of the left ventricular posterior wall in one. Left ventricular outflow obstruction was present in five. The outflow obstruction was unrelated to the degree of respiratory distress and to the severity of the maternal diabetes; it resolved in the first two months of life. Echocardiograms of family members were normal.

One patient died of bacterial sepsis at three weeks of age. Autopsy revealed a hypertrophic septum which distorted both ventricular chambers and bulged into the left ventricular outflow tract. Histologically, hypertrophic fibers, some in a whorling pattern, lay adjacent to necrotic foci in the septum.

Despite clinical and histological similarities, the hypertrophic cardiomyopathy of infants of diabetic mothers differs from other forms of obstructive cardiomyopathy in that it is both transient and non-familial. Treatment with ventilatory assistance and avoidance of positive inotropic agents has been associated with a favorable prognosis.

RADIONUCLIDE VENTRICULOGRAPHY AND TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN CORONARY ARTERY DISEASE.

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Radionuclide ventriculography(RVG) and two-dimensional echocardiography(2DE) were performed at the bedside in the Coronary Care Unit in 30 patients(pts) admitted to the hospital with chest pain suggestive of acute myocardial infarction(AMI). Severity of regional wall motion abnormalities(RWMA) in anteroseptal, apical and inferoposterior regions was assessed by each technique. Global left ventricular function(LVF) was determined by RVG ejection fraction(EF) and in 2DE from a summed score(SS) based on visual assessment of RWMA. There was a linear correlation between EF and SS: EF=87.1-5.0(SS); r=0.76, SEE=12.2. Assessment of RWMA by each technique showed agreement in 82% (74/90) of regions. Areas of paradoxical wall motion, typically apical in location, were detected by both techniques in 4 pts(13%), although 9 pts demonstrated paradox by only one of the methods(RVG 3 pts; 2DE 6 pts). Of 18 pts with documented AMI 29 regions demonstrated pathologic q waves on electrocardiogram. Corresponding RWMA were detected in 25/29 (86%) regions by RVG, and 24/29 (83%) regions by 2DE; 4/5 discordant regions were normal by both techniques. In pts with AMI there was a correlation between peak creatine kinase(CK) levels and LVF:

*p<0.025	EF(mean±SEM)(%)		SS(mean±SEM)	
CK<1000IU/L	58.3±6.9	*	7.00±0.44	NS *
CK>1000IU/L	44.2±6.3	*	9.67±0.85	NS
CK>2500IU/L	26.0±4.5		12.30±0.51	

CONCLUSIONS:1) RVG and 2DE consistently demonstrate RWMA in pts with AMI 2) There is agreement on location and severity of RWMA between both techniques 3) RVG and 2DE assessment of LVF correlate with each other 4) Both correlate with size of AMI as estimated from CK levels

WEDNESDAY, MARCH 8, 1978
PM
ACUTE MYOCARDIAL INFARCTION
2:00 to 5:15

EFFECTS OF PROLONGED NITROGLYCERIN INFUSION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION.

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In order to appreciate the effects of prolonged nitroglycerin (N) infusion in reducing extension, incidence of arrhythmias and hospital mortality of acute myocardial infarction (AMI), 74 patients (pts) with AMI (admitted within 24 hours of the onset of chest pain) were randomized to control (35 pts) or to N treatment (39 pts) group. Pts with initial systolic arterial pressure less than 90 mmHg were excluded from this study. N was initially infused at a rate of 15 µg/mn and the dose slowly increased every 10 minutes until a fall in systolic arterial pressure of 20 mmHg was obtained. The first 12 pts were treated during 24 hours ; since there were only few effects, N was maintained for 5 to 7 days in the 27 other pts. Infusion began 10.1 ± 0.9 hours after the onset of chest pain and the average rate of N was 50.8 ± 3.2 µg/mn. All pts with anterior AMI (24 N and 22 control pts) were studied by 30 lead precordial mapping and the maps recorded on admission and 7 days later were comparatively analyzed. Vulnerable sites were defined as sites with ST segment elevation $\geq$1.5 mm and persistent R wave on initial map. Q waves appeared in 56.2 ± 14.0% of the vulnerable sites in control pts vs 30.0 ± 7.3% in N pts. The sum of R wave voltages (ΣR) in these sites fell more in the control group than in the N group (64.0 ± 12.7% vs 32.4 ± 8.1%, $p<0.05$). Ventricular fibrillation (VF), ventricular tachycardia (VT) were less frequent in the N group (VF : 0, VT : 4) than in the control group (VF : 3, VT :8). The hospital mortality was reduced in the N group : only 2 of 39 pts died versus 8 of 35 control pts ($p<0.05$). Although number of pts was limited, beneficial effects of prolonged N infusion were significant in reducing electrocardiographic extension and hospital mortality of AMI.

BLOOD PRESSURE AND SURVIVAL FOLLOWING MYOCARDIAL INFARCTION: THE FRAMINGHAM STUDY

William B. Kannel, MD, FACC; Paul Sorlie, M.S.; William P. Castelli, MD, Heart Disease Study, Framingham, MA

Blood pressures were obtained routinely on 2336 men in the Framingham cohort followed biennially over a 20-year period. During that time 193 men developed their first recognized myocardial infarction and 126 men developed their first angina pectoris, and were eligible for further prognostic follow-up.

Angina subjects with hypertension after the event had four times the mortality of those who were entirely normotensive, with borderline hypertensives having almost double the normotensive's mortality. Hypertension prior to development of angina pectoris was also associated with an excess 5-year mortality (7-fold). A change in blood pressure was not associated with a significant difference in mortality. On the other hand, for myocardial infarction, blood pressure status after the event was unrelated to subsequent survival. Blood pressure preceding the myocardial infarction was distinctly related to survival, with hypertensives having almost three times the mortality of normotensives. A hypertensive who loses his hypertension following infarction has double the risk of dying of one who shows no change in status. The greater the fall in blood pressure after infarction the greater the mortality over the ensuing years.

Those who experienced a fall in pressure tended to show a fall in vital capacity and a more rapid heart rate. This and the fact that a fall in pressure following uncomplicated angina did not affect mortality suggests myocardial damage as the explanation.

THE EXCELLENT SHORT AND LONG-TERM PROGNOSIS OF PATIENTS WITH SUBENDOCARDIAL INFARCTION

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In acute myocardial infarction (MI), patients (pts) who do not develop new Q waves (no QW) have recently been shown to have a poorer prognosis than pts who do have new Q waves (QW). However, inclusion of pts with prior MI, bundle branch block (BBB) and ventricular hypertrophy (VH) decreases the capability of detecting new QW and produces the possibility that the poor prognosis resulted solely from prior, severe cardiac disease. This study evaluates 96 consecutive pts with no history of MI and no evidence of QW, BBB or VH on admission ECG, in whom the diagnosis of MI was established by at least 3 of the following: 1)elevated total CPK; 2)presence of CPK-MB; 3) $LDH_1 > LDH_2$ and 4)new QW ($\geq$ .03 sec). The results are presented in the table.

	New QW(n=80)	No QW(n=16)
Hospital morbidity	38% (24)	0%
Hospital mortality	6% (5)	0%
Long-term mortality	9% (7)	0%

Hospital morbidity includes ventricular tachycardia or fibrillation, extension of MI, Killip Class $\geq$ III and second or third degree A-V block; the mean follow-up is 31 months and is 100% complete.

Thus, in pts without prior MI, BBB or VH, the prognosis is excellent when acute MI is not associated with new QW.

INFLUENCE OF ASPIRIN ON PLATELET TRAPPING IN MYOCARDIAL INFARCT IN BABOONS

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Platelet trapping (PT) has been demonstrated at the margins of evolving myocardial infarction (MI) in baboons and has been suggested as a reason for evolving necrosis through the marginal zone. Fourteen baboons were subjected to LAD diagonal branch ligation and the extent of myocardial ischemia monitored with a 50-60 electrode epicardial ECG grid. Six animals received no treatment (controls) and 8 animals were pretreated (12 hrs and 1 hr preligation) with aspirin 40 mgm/kg. Infarct extent included all electrode points with >2 mV ST segment increase (ST↑). ^{51}Cr tagged autologous platelets were injected 15 mins prior to ligation. In 6 animals (3 controls, 3 treated) ^{85}Sr labeled radioactive microspheres were used to determine regional left ventricular blood flow 2 hrs postligation. Animals were sacrificed at 6 hrs and tissue blocks from each electrode site and an uninvolved portion of posterior wall, taken for counting. Results: 1) All animals showed ischemia but no differences in ST parameters (number of ST↑ or sum of ST↑) occurred between control and treated groups. 2) 48±3.5% of samples demonstrated PT outside the area of ST↑ in control animals compared with 36±2.3% for treated animals ($p<0.01$). 3) 41±3.2% of samples showed PT outside the area of reduced blood flow in control animals compared with 34±2 for treated animals ($p<0.025$). 4) Extent of endocardial infarction was significantly less than epicardial ($p<0.01$). It is concluded that PT occurs at the margins of myocardial infarcts in primates and can be significantly reduced by pretreatment with aspirin. The implications of these observations on comparing collateral flow to the infarct margin are discussed.

LIMITED EXERCISE TREADMILL TESTING SOON AFTER ACUTE MYOCARDIAL INFARCTION: CORRELATION WITH CORONARY ANGIOGRAPHY AND ANGIOGRAPHIC INDICES OF LEFT VENTRICULAR FUNCTION

Paul H. Dillahunt II, M.D. and Alan B. Miller, M.D., FACC, University Hospital, Jacksonville, Florida

Limited treadmill exercise stress testing (TMET) was performed in 20 patients (pts) at the time of hospital discharge for an acute myocardial infarction (AMI). There were 15 males, average age was 52 years; no pts had congestive heart failure or hypertension. The pts walked at 1 MPH, 0% grade for 5 minutes (negative test) or to an end point of ST-T wave changes, angina, or arrhythmias (positive test). All pts underwent cardiac catheterization including coronary arteriography an average of 8 weeks (range 6-24) following AMI. Parameters of left ventricular (LV) function derived were ejection fraction (EF) and modified LV function curve slopes (S)(ml/min/M^2/mmHg) obtained by plotting cardiac index against LV end diastolic pressure before and after LV angiographic contrast injection. The pts were divided into two groups based on TMET results: Group I (8 pts) with negative tests and Group II (12 pts) with positive tests. Striking differences in distribution of coronary lesions were noted: 75% Group I had single vessel coronary artery disease (>70% obstruction) whereas 83% Group II had 3 or 4 vessel disease. LV function was better in Group I (EF 0.61 $\pm$ 11 vs. Group II 0.42 $\pm$ 13; $p < 0.02$) and S (Group I 72 $\pm$ 19 vs. S Group II 31 $\pm$ 18; $p < 0.001$). We conclude that although coronary arteriography and direct assessment of LV function remain the only definitive methods for assessing the state of LV function and coronary anatomy in pts following AMI, limited TMET performed early after AMI may be useful in predicting the extent of coronary involvement and the amount of LV dysfunction in selected pts.

MYOCARDIAL INFARCTIONS DURING ORAL CONTRACEPTIVE MEDICATION - A DISCRETE DISEASE ENTITY UNRELATED TO CORONARY ATHEROSCLEROSIS?

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Coronary arteriography and left ventriculography were performed in nine premenopausal females who had sustained unequivocal myocardial infarctions (MI) under oral contraceptive medication (OCM) one to 28 (mean: 9) months prior to the study. Left ventriculograms documented segmental akinesis in 5 and hypokinesis in 4 cases corresponding to the ECG and vector locations of MI (5 anterior, 3 inferior, 1 lateral). Coronary arteriograms were normal in 5 patients (PAT) and showed unusual isolated focal smooth lesions (< 30%, 40%, 75% and 90% luminal diameter) in 4 PAT. In one PAT, a 75 % proximal LAD stenosis had regressed to < 30% at a re-study 5 months later. In no case, angiographic evidence of diffuse coronary atherosclerosis was present. Atherogenetic risk factors (cigarette smoking, hyperlipidemia, hypertension, glucose intolerance, positive family history of premature atherosclerosis) of these 9 PAT (group A, mean age 36.8 years) were compared with those of 21 premenopausal women with angiographically advanced coronary atherosclerosis (group B, mean age 37.0 years). Mean number of the above-named atherogenic risk factors in group A was 1.1 (cigarette smoking in 7 of 9 PAT), in group B 3.4 ($p < 0.001$). These data suggest that MI under OCM may be a disease unrelated to coronary atherosclerosis and that OCM act as a contributory factor for MI in rare susceptible women. In analogy to thrombogenetic effects of OCM on peripheral veins and cerebral arteries, occlusion of macroscopically normal coronary arteries by formed elements of blood with a tendency for spontaneous thrombolysis may be assumed to be a pathogenetic mechanism in these MI.

VALIDATION OF INFARCT SIZE PREDICTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

William E. Shell, MD; Marsha Groseth-Robertson, BS; Patricia Rorke, BS, Cedars-Sinai Medical Center, Los Angeles, California

Prediction of infarct size in pts with acute MI is a potentially valuable tool in assessment of clinical therapy. To validate such a concept, we assessed MB-CK and total CK for 72 hrs in pts with acute MI seen within 6 hrs of chest pain. We compared CK observed infarct size (CKIS), MB observed infarct size (MBIS) based on all data points, MB predicted infarct size (MBISP) based on 7 hrs of data, and early MB predicted infarct size (EMBISP) based on 2 hrs of data, in two groups: 1) untreated, "true" control pts, and 2) randomly treated pts. "True" control pts received no vasoactive therapy during the first 48 hrs, while randomly treated pts received multiple therapies, including furosemide, NTG, digitalis, isordil, dopamine, and defibrillation. In "true" controls, MBIS ($\bar{x}$=51.4±13.2 SEM) and CKIS (78.4±20.1) correlated closely (r=.97), in contrast to randomly treated pts where r=.84 (MBIS: 69.8±13.9, CKIS: 94.1±19.5). The correlation of MBIS and MBISP (31.6±11.2) was close in "true" controls (r=.97), as was the correlation between MBIS and EMBISP (48.3±21.3, r=.94). However, in randomly treated pts, the correlation between MBIS and MBISP (44.3±10.7) was only .88, and between MBIS and EMBISP (59.2±14.8), r=.65. Thus: 1) close correlations between MBIS and CKIS in "true" control pts suggest that use of MB values in infarct size estimation is an accurate approximation, 2) close correlations between MBIS, MBISP, and EMBISP in "true" controls suggest that early prediction of infarct size can be implemented in certain groups of pts; 3) lack of close correlations between MBIS, CKIS, and MBISP in randomly treated pts suggest that treatment with vasoactive agents may affect total CK and MB-CK release, and the validity of predictions based on such data.

MECHANISM OF INEFFECTIVENESS OF INTRAMUSCULAR LIDOCAINE IN PREVENTING VENTRICULAR FIBRILLATION.

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In a double blind study we found that 5 of 6 patients(pts) with acute myocardial infarction(AMI)who developed ventricular fibrillation(VF)after intramuscular(IM) administration of 300 mg lidocaine(L)had both low plasma levels(PL) of L and peripheral hypoperfusion(PH). PH was defined as a blood pressure of ≤100 mmHg and a cold and clammy skin. We therefore determined the effect of IML injection on PLL in 14 pts with PH and 6 without PH. All 20 were admitted within 6 hours after onset of AMI. PLL were determined 7, 15, 30 and 60 minutes after IML injection of 300 mg. This procedure was repeated 24 hours later in the same pt when PH was absent in all.

RESULTS: (mean PLL ± SD in ng/ml).

	7 min.	15 min.	30 min.	60 min.
PH on admission	1.8±1.3	2.0±1.1	1.8±0.6	1.3±0.3
24 hours later	2.8±1.4	3.0±1.1	2.6±0.9	1.7±0.5
N=20	p≤0.05	p≤0.025	p≤0.01	p≤0.025
No PH on admission	2.7±1.0	2.4±0.8	1.9±0.4	1.2±0.4
24 hours later	2.8±1.2	2.6±0.7	2.1±0.5	1.5±0.2
N= 6	NS	NS	NS	NS

CONCLUSIONS: 1)Pts with PH on admission have significantly lower PLL in the A phase of MI as compared to those measured 24 hours later after a repeated injection when PH was absent. 2) These differences did not occur in pts without PH on admission. 3)The ineffectiveness of IML injection in preventing VF may be due to PH which prevents adequate PLL to be reached.

ABNORMAL CHRONOTROPIC RESPONSE WITH ACUTE MYOCARDIAL INFARCTION

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Autonomic control of the heart during acute myocardial infarction (AMI) was investigated in fifty subjects, 20 with AMI, 10 with unstable angina, 10 post AMI (3 weeks) and 10 normal volunteers. A computer technique for beat by beat analysis of the R-R intervals was utilized to assess the chronotropic response to respiration (sinus arrhythmia), valsalva and tilt. Atropine (2 mg) and Propranolol (0.1 mg/kg) were administered intravenously for selective and combined autonomic blockade. The extent of left ventricular (LV) injury was estimated by the accumulated release of CK-MB enzyme and by the angiographic ejection fraction (EF). The chronotropic response was abnormal in all patients with AMI. In contrast to the normal sinus arrhythmia of a 15 to 25% R-R interval variation at 12-15 cycles/min, all AMI patients had a slow cyclic (2-4 cycles/min) R-R interval variation of 5 to 20%. The responses to the valsalva and tilt maneuvers were blunted. Patients with small AMI and EF >.4 had a gradual return of the normal chronotropic response within 1-2 weeks, while patients with large AMI and EF <.4 had only a partial recovery at 3-4 weeks. Chronotropic responses after atropine were similar to changes during AMI. The only effect of Propranolol was slowing of the heart rate.

In summary: 1) The chronotropic response during AMI is abnormal with a slow cyclic sinus arrhythmic and a blunted response to the valsalva and tilt maneuvers; 2) The severity and duration of the autonomic disturbance is directly related to the extent of LV injury.

RIGHT VENTRICULAR INFARCTION:CLINICAL FEATURES,EMPHASIZING ITS RESEMBLANCE TO CARDIAC TAMPONADE

Beverly Lorell,MD; Herman K. Gold,MD,FACC; Gerald M. Pohost, MD,FACC; Robert E. Dinsmore, MD,FACC; Robert C. Leinbach, MD,FACC; Adolph M. Hutter, MD,FACC; Roman W. DeSanctis, MD,FACC, Massachusetts General Hospital,Boston, Ma.

Right ventricular infarction (RVI) should be suspected when there is elevation of right-sided filling pressures disproportionate to those of the left heart in the setting of acute myocardial infarction. Although the clinical features of RVI have been described, little attention has been paid to its mimicry of cardiac tamponade. We have studied 14 patients with RVI. All had acute inferior infarction, elevated right-sided filling pressures, and hypotension. 7 had equalization of right ventricular and pulmonary end-diastolic and pulmonary wedge pressures. Pressure tracings showed dramatic early diastolic dip and plateau configurations. 4 of these were thought to have tamponade, and 3 underwent attempted pericardiocentesis. Angiographic and noninvasive studies were helpful in subsequently clarifying the diagnosis. Of the total group, RV cines in 3 and gated cardiac scans in 5 showed RV enlargement and hypokinesis, often with right atrial and left inferoapical ventricular abnormalities. Other notable clinical features included frequent atrial arrhythmias, prolonged heart block, and evanescent pleural effusions. Management consisted of volume replacement, pressors, and in 3, use of intraaortic balloon counterpulsation. There were 5 early deaths from pump failure and 1 late sudden death. Autopsy in 1 confirmed massive RVI.

This experience emphasizes the importance of recognition of RVI. Noninvasive techniques may complement hemodynamic data in differentiating RVI from cardiac tamponade, a condition which it may closely mimic.

RIGHT VENTRICULAR INFARCTION COMPLICATING LEFT VENTRICULAR INFARCTION: A COMPLICATION EXCLUSIVELY OF POSTERIOR WALL INFARCTION.

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In an occasional patient (pt), with acute myocardial infartion (AMI) of the left ventricle (LV) secondary to coronary arterial luminal narrowing, the right ventricular (RV) wall also is infarcted. Surprisingly, no clinicopathologic studies have focused on pts with RV AMI complicating LV AMI. We studied 13 pts at necropsy with RV AMI complicating LV AMI. Their ages ranged from 26 to 82 years; 12 were >55. Nine were men. Three had posterior LV AMI in the past which healed and at necropsy all 3 had healed RV posterior wall infarcts. The other 10 had no myocardial scars. Each had posterior LV AMI with extension to RV posterior wall via the ventricular septum (VS). The RV and LV infarcts in all 13 patients were transmural. No clinical parameters allowed diagnosis of RV AMI during life in any of the 13 pts. None had evidence of chronic pulmonary hypertension. Three, however, had complete heart block (CHB), 4 had rupture of VS and 1 had rupture of LV papillary muscle. Thus, the appearance of a precordial systolic murmur in a pt with AMI involving the posterior ("inferior") wall, particularly if CHB also is present, should arouse suspicion of associated AMI of the RV wall.

WEDNESDAY, MARCH 8, 1978
PM
CARDIOVASCULAR SURGERY IN THE ADULT
2:00 to 5:15

THE EFFECT OF SURGICAL VERSUS MEDICAL THERAPY OF CORONARY DISEASE ON RETURN TO WORK

Karl E. Hammermeister, MD, FACC; Timothy A. DeRouen, PhD; Milton T. English, MD, FACC; Harold T. Dodge, MD, FACC, VA Hospital and University of Washington, Seattle, WA

To determine the relative efficacy of coronary surgery on return to work, all available patients in a coronary angiography registry (Seattle Heart Watch) were assessed by questionnaire. The proportions of medically and surgically treated patients working three months before catheterization or surgery were 74% (148/201) and 75% (899/1198) respectively; while 62% (125/201) and 62% (747/1198) respectively were working full time one year after catheterization or surgery. Subgroup analyses revealed no difference in return to work between medically and surgically treated patients with less than 12 years education, patients in functional class III or IV, patients with two or three vessel disease, and patients doing medium or heavy work. Multivariate analyses demonstrated that work status three months before catheterization or surgery was clearly the major variable predictive of continued employment 15 months later. Over 78% (844/1076) of patients working three months before continued to work 15 months later, while only 12% (36/307) off work three or more months continued to work. Further multivariate analyses designed to test for effect of surgery on return to work while adjusting for effect of functional class, education, and age, demonstrated that mode of therapy (medical versus surgical) had no effect on work status one year after catheterization or surgery (F=0.1). These data indicate that surgical therapy of coronary disease does not improve prospects of continued gainful employment in patients with coronary disease.

EXERCISE TESTING IN THE FOLLOW UP OF PERIOPERATIVE MYOCARDIAL INFARCTION

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The development of a perioperative myocardial infarction during coronary artery bypass surgery is a known complication but its effect on long term mortality and morbidity is not currently understood. To evaluate this problem, we have defined a population of 100 patients, 50 with perioperative infarction and 50 without ECG changes noted postoperatively. They were matched by age, number of vessels grafted, presence of infarction prior to surgery, postoperative graft patency and level of ventricular function. Follow up exercise tests are available in 50 patients, with 20 in the perioperative infarction group. The mean follow up for the whole group was 26.2 months. Results of exercise revealed no difference in the incidence of a positive test for ischemia, presence of arrhythmias or the intraexercise development of hypotension. Although the length of exercise in the non-infarct group was 718 ± 231 seconds and the infarct group achieved a mean level of 576 ± 255 seconds, the difference does not have a P value of less than 0.05. The study demonstrates no difference between the two groups and implies no major long term functional consequence in the group with a perioperative myocardial infarction.

EFFECT OF HYPOTHERMIA AND CARDIOPULMONARY BYPASS ON THE PHARMACOKINETICS OF PROPRANOLOL

Russell G. McAllister, Jr., MD, FACC; David W. Bourne, PhD; Lewis W. Dittert, PhD; Edward P. Todd, MD. VA Hospital and the University of Kentucky Medical Center, Lexington, Kentucky

Propranolol (P) may be useful during cardiac surgery (CS), since pretreatment with this drug prevents the hypokalemia resulting from hypothermia (H) and cardiopulmonary bypass (CPB). Serial plasma concentrations (PC's) of P were measured during CS in 10 patients who had been treated chronically with P. Although no further P was given during CS, P levels (corrected for plasma volume dilution) were significantly higher after only 10 minutes of H+CPB than in the preoperative period (42.5 ± 4.5 vs 30.8 ± 6.8 ng/ml; $p < 0.05$). P PC's remained elevated throughout the CS, falling to or below preoperative values only after rewarming. Precise kinetic analysis of the data was difficult, however, due to the variables inherent in CS. To define the kinetic alterations due to H, intravenous P (1 mg/kg) was given twice to each of six mongrel dogs, first after anesthesia only, then after anesthesia plus cooling to 25°C in a water bath. Serial P PC's were measured in each experiment and the elimination kinetics calculated. Compared with the paired normothermic control studies, H caused a decrease in P half-life (T/2: 73.6 + 15.2 to 45.0 + 10.2 min; $p < 0.01$) and a marked contraction in the volume of distribution (V_d: 6.78 + 1.65 to 2.08 + 0.58 L/kg; $p < 0.001$). The total body clearance of P decreased by half during H. These data suggest that H alone significantly alters the pharmacokinetics of P, both by decreasing the V_d and by slowing the rate of metabolic elimination of the drug. Therefore, small doses of P given prior to H+CPB may produce higher plasma drug levels (and thus effects) than anticipated.

EXERCISE HEMODYNAMIC IMPROVEMENT AFTER AORTA-CORONARY ARTERY BYPASS SURGERY

Ronald E. Vlietstra, MD; James H. Chesebro, MD, FACC; Robert L. Frye, MD, FACC; Robert B. Wallace, MD, Mayo Clinic and Mayo Foundation, Rochester, Minn.

The hemodynamic response to 3 min of 150 kg-m/min supine bicycle exercise (HRE) was measured both before and 3-36 mo (mean 17) after aorta-coronary artery bypass surgery in 39 patients (pts) with significant coronary artery (CA) disease (stenoses ≥75%). HRE was considered to be abnormal if supine resting left ventricular end-diastolic pressure (LVEDP) was >16 mm Hg, with feet up was >19 mm Hg, or exercise increase in LVEDP was >5 mm Hg. In 32 pts the preoperative (preop) HRE was abnormal; postoperatively (postop) 11 of these 32 became normal (Gp N), whereas 21 remained abnormal (Gp A). Mean (± SD) LVEDPs (mm Hg) were:

	Preop			Postop		
	Gp N	Gp A	P	Gp N	Gp A	P
Supine rest	15 ± 5	16 ± 4	>0.5	12 ± 3	17 ± 5	<0.01
Feet up	18 ± 3	18 ± 5	>0.5	14 ± 3	19 ± 5	<0.01
Exercise	32 ± 5	31 ± 7	>0.5	16 ± 5	28 ± 7	<0.001

Gps N and A did not differ significantly in preop LVEDPs (above) or in mean stroke work index at rest (58 vs. 65 gm-m/m^2, respectively), with feet elevated (58 vs. 65), or with exercise (57 vs. 60); nor did they differ in mean ejection fraction (62 vs. 64%), number of vessels with CA disease (3.2 vs. 3.4, 5-vessel scale), or number of CA bypass grafts (1.5 vs. 1.8). However, a significant ($P<0.01$) difference was noted in the frequency of complete left CA revascularization (8/11 in Gp N and 4/21 in Gp A). Gp N had a high incidence of asymptomatic pts (10/11) postop, but there was no significant difference between mean preop (62%) and postop (67%) ejection fractions. Thus, postop improvement in HRE is largely determined by completeness of left CA revascularization and may occur despite little or no change in the ejection fraction.

EXTRACRANIAL CAROTID OCCLUSIVE DISEASE AS A RISK FACTOR IN CARDIOVASCULAR SURGERY

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The coexistence of extracranial carotid occlusive disease increases the risk encountered in performing major cardiovascular surgery, especially if systemic hypotension may occur during or after surgery. Reduction of internal carotid blood flow secondary to extracranial carotid occlusive disease is reliably determined pre-operatively by oculoplethysmography (OPG), the noninvasive comparative timing of simultaneously recorded ocular pulse waveforms. OPG studies were performed on patients being evaluated for 216 cardiovascular procedures consisting of 78 cardio-thoracic, 64 aortic, and 74 peripheral arterial operations. Negative OPG studies were obtained in 144 cases with subsequent non-carotid surgery resulting in two strokes due to emboli. Of the 72 positive OPG evaluations, 35 first underwent carotid endarterectomy and then the other cardiovascular surgery without neurologic sequelae. One patient with positive OPG studies evolved a frank stroke the day before his scheduled aortic aneurism surgery. Of the other 36 patients with positive OPG studies who had non-carotid cardiovascular operations, seven (19%) incurred surgery related strokes. The safety and reliability of OPG makes its use desirable prior to any angiography in anticipation of cardiovascular surgery to determine those patients for whom concurrent carotid arteriography should be performed. If clinically feasible, priority should be given to carotid endarterectomy before undertaking other cardiovascular procedures when significant internal carotid blood flow reduction indicative of extracranial carotid occlusive disease is detected by oculoplethysmography.

REDUCTION OF INTIMAL THICKENING IN CANINE CORONARY ARTERY BYPASS VEIN GRAFTS WITH DIPYRIDAMOLE AND ASPIRIN

Michael P. Metke, MD, J. T. Lie, MD, FACC, Valentin Fuster, MD, Miguel Josa, MD, Michael P. Kaye, MD, FACC, Mayo Clinic and Foundation, Rochester, MN

The potential benefit of antiplatelet drugs on coronary artery bypass vein grafts (VGS) was assessed in 20 dogs. Two dogs died 2 hr postop. In the 18 remaining dogs, magnification corrected angiographic luminal measurements, platelet survival (^{51}chromium labeling) and quantitative histologic examination of VGS was performed. There were 9 control animals and 9 animals treated with dipyridamole (2.5 mg/kg/day) plus aspirin (15 mg/kg/day) (D+ASA). All animals lived to elective sacrifice at 2, 4 or 6 mo with 100% graft patency. At 14 days, greater angiographic narrowing occurred in the most distal 1 cm of vein grafts of controls than D+ASA dogs ($p < .01$). There was no difference in the most proximal 1 cm of VGS. This same angiographic narrowing persisted in control dogs until the time of sacrifice ($p < .03$). Computer assisted measurements of the entire area of intimal thickening were done on vein graft cross sections taken 1 cm from the distal anastomosis. The circumference of the VGS at the medial-intima junction was measured from the same section and the potential luminal area calculated. The calculated luminal narrowing due to intimal thickening was greater in controls than in D+ASA dogs ($p < .03$). These data correlate well with the demonstrated angiographic narrowing. In a separate group of dogs, platelet survival was $1.9 \pm .44$ days in controls and prolonged to $2.3 \pm .03$ days in D+ASA dogs. One animal caused the large standard deviation in the control group. His platelet survival was 3.0 days. He had minimal intimal thickening at 6 mo. Our data indicate that early intimal thickening that persists 2 to 6 mo postoperatively in canine coronary artery bypass VGS is reduced by the platelet inhibitor combination of D+ASA.

SURGICAL IMPLICATIONS, RISK-BENEFIT ANALYSIS, AND LONG-TERM RESULTS OF COMBINED AORTIC VALVE REPLACEMENT AND MYOCARDIAL REVASCULARIZATION

*=p<0.05

D. Craig Miller, MD, FACC, Edward B. Stinson, MD, FACC, Philip E. Oyer, MD, Norman E. Shumway, MD, FACC, Stanford University Medical Center, Stanford, California.

To better define the indications for and the results of simultaneous aortic valve replacement(AVR)and coronary artery bypass grafting(CABG)a cohort of 271 patients(pts) with angiographically defined absence or presence of CAD undergoing AVR with xenograft bioprostheses was analyzed. Topical hypothermia alone was used for myocardial protection. Followup(321 pt yr)was carried out to 4.8 yr max; mean 1.7 yr.132 pts(49%)had CAD of which 101 had CABG and 139 pts(51%)had no CAD. Subdividing according to functional Ao valvular lesion(predominately AS)gave a homogeneous subpopulation of 212 pts(106 with and 106 without CAD with 87 undergoing AVR+CABG). The CAD subgroup was sig* older with more angina, prior MI, LV dyssynergy, hypertension, and male predominance. No sig* difference existed for CHF, NYHA class, LVEDP, CI, or peak gradient. Peri-op MI and low output were sustained more frequently* by those pts with CAD(9.8%vs0.7% and 44%vs30%)as was hospital death(8.3%vs2.2%; total cohort 14/271=5.2%). Late residual angina and MI also correlated* with the presence of CAD pre-op. Actuarial survival(excluding hospital deaths)and late functional results were not sig* greater for the CAD pts. Conclusion: CAD occurs substantially in pts undergoing AVR and argues for pre-op angio. Pts with CAD represent increased surgical risk. Moreover, late survival expectations and functional results for discharged pts appear to be as good as those pts without CAD if AVR+CABG is performed. It is only inferred that simultaneous AVR+CABG is responsible for these results which compare very favorably with other reported series. Based on the trends which exist in this analysis, it is prudent to perform simultaneous AVR and CABG if CAD is present.

PREVENTION OF ANASTOMOTIC NEOINTIMAL FIBROUS HYPERPLASIA IN FEMORAL ARTERY BYPASS GRAFTS BY ASPIRIN AND DIPYRIMADOLE

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The University of Rochester Medical Center, Rochester, New York

Neointimal fibrous hyperplasia (NFH) at the anastomoses of prosthetic vascular grafts is a reparative process initiated by a platelet - fibroblast interaction in response to flow induced intimal injury. The effect of Aspirin and Dipyrimadole, drugs which prevent platelet adherence, aggregation and release, on the formation of NFH was examined.

Knitted Dacron internal velour (DIV) and expanded PTFE (Gore-Tex) were used to bypass short segments of the femoral artery in 24 dogs. These animals were divided into two groups; the control group of fifteen dogs (30 grafts, 15 DIV and 15 Gore-Tex) received no medication and the treated group of nine dogs (18 grafts, 9 DIV and 9 Gore-Tex) received 100 mg of Dipyrimadole per day starting four days prior to operation.

All 18 grafts in the medicated group remained patent at 4 months without evidence of NFH.

In contrast, in the control group at 4 months, NFH at the proximal anastomosis resulted in occlusion of 10 of 30 grafts and in anastomotic stenosis of 7 of the remaining 20 patent grafts. This.difference in patency rates was statistically significant at the $p<.01$ level.

AORTIC VALVE REPLACEMENT WITH MYOCARDIAL REVASCULARIZATION

James V. Richardson, M.D., James O. Wright III, M.D., Nicholas T. Kouchoukos, M.D., FACC, Robert B. Karp, M.D., FACC
University of Alabama, Birmingham, Alabama

Aortic valve replacement (AVR) with aortocoronary bypass grafting (ACBG) was performed in 220 consecutive patients (pts) between Jan., 1970 - June, 1977. Preoperatively, 80% were NYHA class III or IV; 172 (78%) had angina. The mean number of arteries with > 50% stenosis was 2.1/pts and the mean number of grafts inserted was 1.8/pts. Early (30 days) mortality (EM) was 5.5% (12 pts). EM was not related to NYHA class, number of bypasses, duration of cardiopulmonary bypass or ischemia or valvular lesion, but was significantly affected by definite peri-operative myocardial infarction (POMI) (no POMI, EM = 2.6%, definite POMI, EM = 17.4%, $p < .01$). Definite POMI, defined by ECG evidence of infarction and significant enzymatic elevation, occurred in 23 pts (11%). Probable POMI, defined by enzymatic elevation only, occurred in 66 pts (32%). Incidence of POMI was not related to the number of bypasses or valvular lesion, but was related to the type of myocardial preservation used. Definite POMI occurred in 24.4% (10/41 pts) who had coronary perfusion and in 8% (13/142 pts) with hypothermic ischemic arrest ($p < .0005$). Definite POMI declined from 25% in 1970-73 to 8.2% in 1974-77 ($p < .01$). Mean follow-up in 100% of patients was 22.5 months (range 1-84 months). Late mortality was 11.5% (24 pts). Cumulative survival was 88% at 1 year and 77% at 3 years. Seventy-five percent of survivors were class I or II. Late survival was not related to NYHA class, number of bypasses or POMI. These data indicate that combined AVR and ACBG can be performed with an EM and late survival similar to AVR alone; POMI is related to the type of myocardial protection used and significantly affects EM.

AORTIC VALVE REPLACEMENT AND MYOCARDIAL REVASCULARIZATION: EARLY MORTALITY

Ronald N. Riner, MD; Abdul J. Tajik, MD, FACC; Robert B. Wallace, MD; Robert L. Frye, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minn.

The purpose of this study was to determine (1) the frequency of coronary artery disease (CAD), as determined by preoperative coronary angiography, in patients (pts) undergoing aortic valve replacement (AVR) for aortic stenosis or aortic insufficiency (or both) and (2) if CAD was present, whether coronary artery bypass grafting (CABG) in addition to AVR influenced early mortality (≤30 days postoperatively). Pts with endocarditis, AVR reoperation, combined valvular surgery, inadequate coronary angiography, associated aortic aneurysms, or congenital heart disease were excluded. A total of 379 pts were reviewed; 181 pts (48%) had CAD (≥50% luminal stenosis). On the basis of management, 3 groups emerged: group A--pts with AVR and no CAD; group B--pts with AVR + CAD; and group C--pts with AVR + CAD + CABG.

	Group A (n=198)	Group B (n=68)	Group C (n=113)
Dead	9	7	8
Alive	189	61	105
Mortality	5%	10%	7%

The mortality in the entire group of pts undergoing AVR without CABG, irrespective of the coronary anatomy, was 6.0%. The differences in mortality between each of the groups outlined above (A vs. B, A vs. C, A vs. B + C) were not statistically significant ($P>0.05$). In conclusion, our study indicates that (1) of 379 pts who had preoperative coronary angiography, 181 (48%) had at least one narrowing (≥50%) of a major coronary artery and (2) the risk of early mortality in pts having isolated AVR as compared with AVR + CABG is not significantly different.

CLINICAL EXPERIENCE WITH INTRALUMINAL MANAGEMENT OF ACUTE MASSIVE PULMONARY THROMBOEMBOLISM, Lazar J. Greenfield, MD, F.A.C.C., J. James Zocco, M.D., William Scoggins, M.D., Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

Controversy over management of massive thromboembolism producing shock and need for vasopressor support is due in part to low survival rates following open embolectomy on cardiopulmonary bypass. As an alternative, a cup-catheter device has been developed for extraction of emboli under local anesthesia via the femoral vein. Initial experience with a balloon-tipped catheter in 10 patients resulted in embolectomy in 9 and improvement in 8; but 2 deaths resulted from recurrent embolism and 1 late death occurred from sepsis. Addition of a new vena caval filter and of directional control of the catheter improved the results in 12 additional patients. Emboli were removed in 10 of them and resulted in improved PaO_2 and cardiac output, and cessation of vasopressors. There were 2 deaths (17%) and complications included bleeding, infarction, transient arrhythmias, and wound infections in a total of 28%. Overall embolectomy rate is 86% and overall mortality from all causes is 32%. Sequential hemodynamic studies during embolectomy show a threshold for restored effective cardiac output, sensorium and urine output despite residual emboli. The ability to extract emboli at the time of angiographic diagnosis avoiding general anesthesia, thoracotomy and cardiopulmonary bypass in these critically ill patients offers improved survival in hospitals with or without capability for cardiopulmonary bypass.

(see Addendum, p 447)

WEDNESDAY, MARCH 8, 1978
PM
ISCHEMIC HEART DISEASE
2:00 to 5:15

ASSESSMENT OF COLLATERAL CIRCULATION AND LEFT VENTRICULAR FUNCTION IN THE POST MYOCARDIAL INFARCT PATIENT BEFORE AND AFTER PHYSICAL TRAINING

Andre Nolewajka, MD; William J. Kostuk, MD, FACC; Peter Rechnitzer, MD, FACC; D. Cunningham, PhD, University Hospital, London, Ontario.

The effect of cardiovascular training on the development of intercoronary collateral circulation and improvement of left ventricular (LV) function in patients (pts)who have survived acute myocardial infarction (AMI) remains controversial. Pts (17 males, mean age 49, range 32-54) who were convalescent from an AMI underwent a physical training exercise programme (PTEP) (6 pts) or participated in recreational activities with no training effect (11 pts). Both groups underwent selective coronary angiography, LV function studies and intracoronary myocardial perfusion studies with labelled microspheres both before and after the 7 month experimental programme. The extent of angiographically graded disease was similar in both groups with no change occurring in coronary anatomy, myocardial perfusion or LV function in either group. Although only the PTEP group showed an increase in anginal threshold together with a decrease in heart rate at a given work load ($P< 0.05$) both groups developed a positive attitude towards their disease. PTEP does not effect the progression of disease, does not lead to the development of intercoronary collateral vessels and does not alter left ventricular function in post myocardial infarction pts.

CORONARY ANGIOGRAPHY IN THE EARLY POST MYOCARDIAL INFARCTION PERIOD. Jon D. Turner, M.D., William J. Rogers, M.D., FACC, Charles E. Rackley, M.D., FACC, John A. Mantle, M.D., FACC, Richard O. Russell, Jr., M.D., FACC. UAB Med Ctr, Birmingham, AL.

The safety and value of coronary angiography in the early post myocardial infarction (MI) period has not been established. To assess the safety and value of the procedure, the records of 68 consecutive patients (pts) who underwent coronary angiography and left ventriculography within 30 days (mean=21.8) after acute MI were evaluated. 34 pts had a complicated post MI course: 19 had post-MI angina (2 unstable); 13 had congestive heart failure (CHF); and 12 had persistent ventricular arrhythmias (PVA) requiring treatment. Ventricular tachycardia during angiography occurred in 2 of the 4 pts with both post-MI angina and PVA. Additional myocardial necrosis occurred after angiography in 1 pt with CHF and unstable angina. There were no other serious complications. Coronary angiography revealed significant stenosis (≥70%) in the following distribution: 6 (9%) left main (LM); 23 (34%) three-vessel (3V); 20 (29%) two-vessel (2V); and 19 (28%) one-vessel (1V). LM or 3V disease was found in 16/34 (47%) of the complicated group and in 13/34 (38%) of the uncomplicated group (p=NS). Of 20 pts with previous MI, 12 (65%) had LM or 3V disease compared to 17/48 (35%) without previous MI (p=NS). Candidates for saphenous vein bypass grafting, defined by LM or 3V disease with distal vessels to non-infarcted areas ≥ 3mm diameter and ejection fraction ≥ .30, were identified in 8/16 (50%) of the complicated group and in 7/13 (54%) of the uncomplicated group. Conclusions: 1) Coronary angiography and ventriculography can be performed safely within 30 days after MI in the stable pt and with mild risk in the pt with post-MI complications. 2) Subgroups of pts with LM or 3V disease occur in a significant percentage of both complicated and uncomplicated MI. 3) Pts with LM or 3V disease cannot be prospectively identified by the presence or absence of previous MI or by the clinical post-MI course.

IDENTIFICATION OF HIGH RISK CORONARY DISEASE BY MYOCARDIAL PERFUSION SCINTIGRAPHY DURING EXERCISE TESTING.

Barry Massie, MD; Harold Dash, MD; Elias Botvinick, MD; Bruce Brundage, MD, FACC; David Shames, MD; University of California, San Francisco, California.

The noninvasive detection of patients (PTS) with left main (LM), LM equivalent (LME) or 3-vessel (3-V) coronary disease (CAD) has become increasingly important because of their high risk and the growing use of corrective surgery in these PTS. The presence of a markedly positive (MP) treadmill exercise test (ET) (≥2mm ST segment depression earlier than 6 minutes of the Bruce Protocol) while helpful, has not been sufficiently sensitive or specific. To assess the accuracy of stress perfusion scintigraphy (SPS) in the diagnosis of high risk CAD we reviewed the SPS of PTS with either high risk lesions or 1-or2-vessel (1-or2-V) disease. SPS was MP and diagnostic of LM or LME if posterolateral and septal or anterior defects were seen, and MP and indicative of 3-V disease if radioactivity was seen only at the base of the heart with poor distal uptake.

	LM (N=7)	LME (N=9)	3-V (N=16)	1-or2-V (N=20)
MPET:	2	5	4	6
MPSPS:	3	4	6	1
MPET or MPSPS:	5	7	9	7

MPSPS and MPET was similarly sensitive in detecting high risk CAD, but MPSPS was more specific in defining these PTS (only 1/20 false positive vs 6/20). The combined use of both tests improved sensitivity ($p<0.05$) detecting 21/32 PTS vs 11/32 by MPET alone. SPS was positive in all but 1/32 PTS while 11/32 had negative ET ($p<0.01$), demonstrating that SPS is more sensitive than ET in detecting the presence of CAD in PTS with high risk lesions. Our results indicate that there are scintigraphic patterns characteristic of LM, LME and 3-V disease and that SPS is a useful adjunct in the identification of PTS with high risk CAD.

COMPARISON OF THE EFFECTS OF ISOPROTERENOL AND OUABAIN ON REGIONAL FUNCTION, FLOW AND ELECTROGRAMS OF ISCHEMIC MYOCARDIUM OF CONSCIOUS DOGS.

Stephen F. Vatner, MD, Hank Baig, MSEE, W. Thomas Manders, BS and Paul A. Murray, PhD, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts.

The goal of this study was to compare the action of two positive inotropic agents with different mechanisms of action, e.g., isoproterenol and ouabain, on ischemic myocardium of conscious dogs. Instrumentation included flow probes and occluders on a branch of the left coronary artery, miniature ultrasonic transducers implanted in the potentially ischemic zone of myocardium to measure regional segment length and electrograms, and arterial and atrial catheters for measurement of regional myocardial blood flow (radioactive microsphere technique). Coronary occlusion 2-4 weeks after operation reduced segment length in the ischemic zone from 2.69±.31 to -.26±.09 mm, i.e., paradoxical bulging appeared, and flow fell by 77±4% while ST segment elevation rose by 9.1±0.7 mV. Isoproterenol, .4 μg/kg/min, i.v., in 12 dogs augmented the extent of paradoxical bulging to -.69±.09 mm ($p<.01$) and ST elevation by 3.9±0.2 mV ($p<.01$), while blood flow did not change significantly. In contrast, 15 min. after 12 other dogs were given ouabain, 20 μg/kg i.v. bolus, regional function improved, i.e., segment length shortening rose by 0.35±0.10 mm ($p<0.01$), blood flow rose by 46±9% ($p<0.01$) and ST elevation fell by 3.1±0.3 mV ($p<0.01$). In conclusion, two potent inotropic agents with different mechanisms of action exert diametrically opposite effects on ischemic myocardium of conscious dogs. On the one hand, a strong beta-adrenergic agonist, e.g., isoproterenol, increases paradoxical bulging and ST segment elevation. On the other hand, a cardiac glycoside reduces ST segment elevation and enhances regional myocardial function and blood flow.

REST AND STRESS THALLIUM 201 IMAGING IN LEFT MAIN CORONARY DISEASE: SENSITIVE BUT NOT SPECIFIC.

Terry Rehn, MD; Lawrence Griffith, MD, FACC; Stephen Achuff, MD; Bernadine Bulkley, MD, FACC; Malcolm Pond, MD; Lewis Becker, MD, FACC. Johns Hopkins University, Baltimore, Maryland.

Nineteen patients (pts) with left main (LM) coronary artery disease (CAD) received rest and stress Thallium (TL) scans to determine the sensitivity of TL imaging and whether a coincidence of image defects in the distribution of both the left circumflex (Circ) and anterior descending (LAD) coronary artery (CA) was a predictor of LMCAD. Images were analyzed by vascular areas (VA) (LAD, Circ and right coronary artery) for 161 pts with catheterization proved CAD as defined by >50% luminal coronary stenosis. Nineteen pts with LMCAD (Group A), 15 of whom also had significant disease in all three coronary arteries were compared with 12 pts with LAD and Circ CAD (Group B), 44 pts with LAD, Circ and right CAD (Group C) and 161 pts with CAD (Group D).

Group	Abnormal Rest Image	Abnormal Rest or Stress Image	LAD and Circ Defects
A (n=19)	18 (95%)	19 (100%)	3 (42%)
B (n=12)	9 (75%)	11 (92%)	2 (17%)
C (n=44)	33 (75%)	44 (100%)	10 (23%)
D (n=161)	102 (64%)	142 (88%)	24 (15%)

The sensitivity of TL stress imaging in both 3 vessel CAD and LMCAD was 100%. The mean number of VA involved for LMCAD was 2.2 and for 3 vessel CAD was 2.3. The pattern of LAD and Circ was common in LMCAD, appearing in 42% of pts, but the predictive value of this pattern was only 33% (8/24).

The results show that TL imaging is highly sensitive for detection of CAD in pts with LM disease but the pattern of image defects is not specific for the anatomic lesion.

COURSE OF ARTERIAL AND PULMONARY WEDGE PRESSURES AFTER ACUTE MYOCARDIAL INFARCTION: EFFECT OF NITROPRUSSIDE

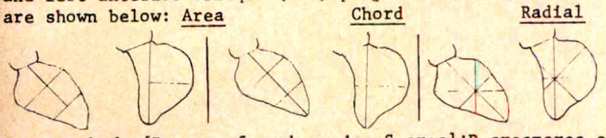
Joseph A. Franciosa, MD, FACC; Jay N. Cohn, MD, FACC; Donald Archibald for VA Cooperative Study Group, Minneapolis, Minnesota.

Nitroprusside (N) infusion in patients with acute myocardial infarction (AMI) reduces systemic and pulmonary arterial pressures. Since hypotension could impair coronary perfusion, it has been suggested that the fall in systemic pressure could be harmful. A continuing VA Cooperative Study randomizes AMI patients double-blind to a 48-hour of infusion of N or placebo (P). Pressures in the 2 groups (91 N, 104 P) were monitored at 8 hour intervals before, during and after the infusion. Systolic arterial pressure (SAP) and pulmonary artery diastolic or wedge pressure (PWP) were similar in the pretreatment period in the N and P groups (133.8 vs 134.9 mm Hg and 20.6 vs 21.1 mm Hg). After 8 hrs of infusion SAP and PWP were reduced more ($p<.01$) in N (16.4 and 6.2 mm Hg) than in P (10.4 and 3.3 mm Hg). Heart rate (HR) was unchanged. From 8 to 24 hrs SAP and PWP were stable in N group but fell in P group so that by 24 hrs values were again similar in the N and P groups (N: 117.6 and 14.3 mm Hg, P: 118.6 and 15.0 mm Hg). At 48 hrs SAP and PWP were at similar levels in the two groups (N: 114.0 and 12.8 mm Hg, P: 112.1 and 13.6 mm Hg). After the infusions were stopped pressures remained at similar levels in the two groups. N thus reduces SAP and PWP acutely, achieving a level of SAP higher than is later reached in the P group. Therefore, N merely accelerates the natural fall in pressures after AMI.

DETECTION OF LEFT VENTRICULAR REGIONAL WALL MOTION ABNORMALITIES: COMPARISON OF AREA, CHORD AND RADIAL METHODS.

H. Gelberg, MD; B. Brundage, MD, FACC; S. Glantz, PhD; S. Rubin, MD; T. Hiyashi, PhD; W. Parmley, MD, FACC; University of California, San Francisco, California.

A universally accepted system for evaluation of left ventricular (LV) wall motion abnormalities (WMA) on ciné ventriculogram (Vgram) has not been devised. We examined 3 systems of WM analysis using biplane Vgram prior to automating one system for clinical use. We established normal ranges (i.e., within 2 standard deviations [StDV]) for each system in each region of the LV using 10 Vgrams of patients with normal coronary arteriograms and no WMA. We examined 7 Vgrams of varying degrees of WMA. All methods are: based on percent change (Δ) from end-diastole (D) to end-systole (S); take into account normal systolic anterior rotation; and, examine the right anterior oblique (RAO) and left anterior oblique (LAO) projections. The methods are shown below: Area Chord Radial



Area method: [D area of each region-S area]÷D area=area ejection fraction. Chord and radial methods: [D length of line-S length]÷D length=ejection fraction shortening. The changes with ejection were normalized in each method by: [Δ-mean change of a given normal region]÷StDV for that region (i.e., Z score). The largest Z score would indicate the greatest separation between normals and abnormals. The average abnormal region was 2.3 StDVs from the normal by the area method but only 1.4 by the chord and 1.1 by the radial methods.

The area method is most sensitive in detecting LV WMA and therefore this system was selected and programmed on a desk top calculator for clinical use.

ULTRASTRUCTURAL CHANGES OF ISCHEMIC MYOCARDIUM IN PATIENTS WITH THE INTERMEDIATE SYNDROME

Monty M. Bodenheimer, MD, FACC; Vidya S. Banka, MD; Robert G. Trout, MD, FACC; George Hermann, MD; Homayoon Pasdar, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

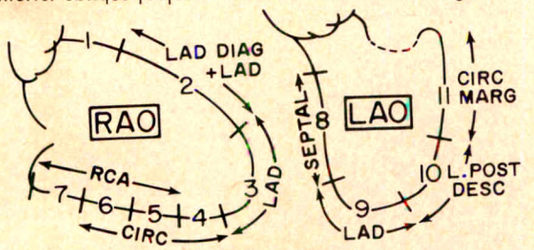
To better understand the state of the myocardium in patients with the intermediate syndrome (ST-T wave changes, chest pain of ≥24 hrs, normal enzymes and no new Q waves) transmural biopsies were obtained at the time of open heart surgery in 8 pts from the ischemic area as demarcated on epicardial electrograms prior to bypass. All pts had similar light and electron microscopic findings distributed transmurally. Light microscopy revealed prominent hypercontraction bands. There was no evidence of coagulation necrosis or acute inflammatory responses. Ultrastructurally, all areas examined displayed varying stages of fiber contraction with no I bands discernible. Electron dense, amorphous contraction bands derived from collapsed Z band areas irregularly interrupted the orderly cross striation of the fibers. Intra and extracellular edema displaced both muscle fibers and individual myofibrils exhibiting focal myofibrillar dissolution. Scattered eosinophilic dense bodies, often membrane bound, commonly showed close association with swollen, atypical mitochondria. Vacuolated foci frequently punctuated the mitochondria. Myocardial fiber nuclei displayed peripherally condensed chromatin. Small vascular channels were unaffected and glycogen was not notably depleted in most areas. Post-operatively none of the 8 pts developed Q waves. Thus, patients with the intermediate syndrome ultrastructurally manifest myofibrillar degeneration consistent with experimental electron microscopic findings in the periphery of ischemic or reperfused myocardium.

SEGMENTAL LEFT VENTRICULAR AKINESIS IN SINGLE VESSEL CORONARY DISEASE.

Lawrence Griffith, MD, FACC; Louise Grunwald; Joseph Gerry, MD; Stephen Achuff, MD; Johns Hopkins University, Baltimore, Maryland

Segmental left ventricular akinesis(LVA) can be correlated with ≥ 70% narrowing of the left anterior descending(LAD), right(RCA) or left circumflex(CIRC) coronary artery(CA).

Fifty-six patients(pts) with single vessel disease(SVD)(one artery narrowed ≥ 70%, other arteries < 40%) and one or more LVA segments were studied. LV angiographic silhouettes in right and left anterior oblique projections were divided into 11 segments:



Patients With Akinetic Segment

	Seg. No.	1	2	3	4	5	6	7		8	9	10	11
LAD	28pts	1	23	21	0	0	0	0	22pts	10	21	0	0
RCA	21pts	0	0	0	6	13	18	19	12pts	0	0	11	0
CIRC	7pts	0	0	0	2	6	6	0	7pts	0	0	4	4

LVA in pts with SVD-LAD was limited to segs 2,3,8,9 ($P < 0.01$). In SVD-RCA, 18/21 had LVA of seg 6, 7. In SVD-CIRC, 6/7 had LVA of segs 5,6. LVA of seg 10 correlated with disease of the left posterior descending branch of either RCA or CIRC ($P < 0.001$). In SVD-CIRC marginal, LVA is limited to seg 11 ($P < 0.001$).

This correlation between segmental LVA and the perfusing CA has proved useful in assigning priorities for coronary bypass by estimating the "viability" or scar replacement in the distribution of a narrowed coronary artery.

ALTERATIONS IN CALCIUM CONTENT OF CORONARY SINUS BLOOD DURING CORONARY ARTERIOGRAPHY. ACCENTUATED MYOCARDIAL DEPRESSION BY CONTRAST MATERIAL IN THE PRESENCE OF HYPOCALCEMIA.

Charles B. Higgins, M.D.; Walter Schmidt; University of California, San Diego, California.

Electromechanical dissociation is a rare but fatal complication of coronary arteriography. Since electromechanical dissociation is a known consequence of hypocalcemia, we investigated the variations in coronary sinus total (T) (fluorometric method) and ionic (I) calcium (C) (ion specific electrode) during coronary arteriography in 17 dogs. Renografin (R) (no calcium ions) induced decreases in dp/dt (-29 ± 4%) $dp/dt/LVP_{40}$ (-18 ± 4%), TC (-36 ± 3%), IC (-47 ± 6%), and hematocrit (-47 ± 5%). IC/TC decreased (-15 ± 4%) during peak opacification suggesting chelation by R. After induced hypo Ca (EDTA infusion) and myocardial depression (pentobarbital), the above parameters declined to a greater extent, persisted longer, and in 10 dogs with hypo C caused prolonged hypotension and pulsus alternans. Isopaque 370 (contains Ca++) increased dp/dt (+28 ± 1%) $dp/dt/LVP_{40}$ (+20 ± 4%), IC (+7 ± 2%), IC/TC; and decreased TC (-9 ± 2%) and hematocrit. The positive inotropic effect was greater in the presence of induced hypo Ca and myocardial depression. Thus currently used contrast material causes myocardial hypo Ca by a dilutional and chelating effect, which contributes to the negative inotropic effect. Ca++ containing contrast material reverses these effects.

MYOCARDIAL HYPOXANTHINE RELEASE: A BETTER MARKER OF MYOCARDIAL ISCHEMIA?

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Early myocardial hypoxanthine (H) release has been found to be an early indicator of ischemia in experimental animals. In order to test whether H is a better indicator of ischemia than lactate (L) in man, arterial and coronary sinus H and L were determined during atrial pacing stress in 24 patients (pts). Left ventricular pressure (LVP), measured by tip manometer, and its first derivative (dP/dt) were also measured. Pacing-induced angina (A) occurred in 17, whereas no anginal symptoms (NA) could be provoked in the other 7 pts. No significant differences in maximum pacing-induced heart rates (135 vs 140 beats/min), LVP and dP/dt were found in both groups. Arterial concentrations of H (1.0 ± 0.4 μM) and L (0.6 ± 0.2 mM) did not change in A and NA pts. Control values of coronary sinus concentrations of H and L were the same in both groups and did not change during pacing in NA pts. In pts with A, coronary sinus H increased from 1.2 ± 0.5 to 1.9 ± 0.5 μM ($p<0.001$) and L from 0.6 ± 0.2 to 0.8 ± 0.3 mM ($p<0.005$). H release (arterial: 0.87 ± 0.10 μM, coronary sinus: 1.33 ± 0.08 μM, $p<0.001$) persisted five minutes after pacing, whereas L returned to control values.

We conclude that H is a more sensitive, and longer lasting indicator of pacing-induced myocardial ischemia than L.

DISPARATE EFFECTS OF PHENYLEPHRINE-INDUCED ACUTE BLOOD PRESSURE ELEVATION ON EXTENT OF VENTRICULAR ISCHEMIA IN PORCINE VERSUS CANINE MYOCARDIAL INFARCTION

James M. Foerster, MD; Zakauddin Vera, MD; David Janzen, BS; Dean T. Mason, MD, FACC, University of California, Davis, California

Most experimental myocardial infarction (MI) drug studies have used canine models, although pig coronary anatomy more closely resembles the human. We have previously validated the use of Frank XYZ lead ST magnitude to substitute for the sum of ST epicardial grid segments in assessment of myocardial ischemia. Seven pigs and four dogs underwent thoracotomy, coronary snare placement, and chest closure. Frank XYZ leads were attached. At least 40 minutes after coronary ligation, ST magnitude rise (STM) was measured and plotted against systemic arterial blood pressure (BP) following increased intravenous dosage of phenylephrine.

	Control $\overline{BP}$	$\overline{BP}$ at Minimum STM	Minimum STM: % Control
Pig	78	*97	*86%
Dog	96	*149	*39%

*$p<.01$ compared to control. $\overline{BP}$ = mean blood pressure (mm Hg). Porcine myocardial infarction STM showed a biphasic response to BP changes; STM increased at both the low and high end of BP spectrum and was least elevated at middle BP range (average 97 mm Hg). In contrast, canine MI had least STM at highest attained BP (average 149 mm Hg), apparently due to more extensive preformed coronary collaterals than in the pig heart. This divergent response of STM to BP elevation focuses attention on type of animal model utilized for extrapolating results of pharmacologic and related interventions in experimental acute myocardial infarction to man.

WEDNESDAY, MARCH 8, 1978
PM
CARDIOVASCULAR PHARMACOLOGY
2:00 to 5:15

COMPARISON OF THE IMMEDIATE EFFECTS OF FIVE BETA RECEPTOR ANTAGONISTS WITH DIFFERENT ANCILLARY PROPERTIES IN ANGINA PECTORIS.

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The comparative activity of propranolol (P), oxprenolol (Ox), Practolol (Pra), Metoprolol (Met), and Tolamolol (Tol) was compared against placebo (PL) in 12 patients (pts) with stable exertional angina pectoris (AP). Heart rate (HR), ST segment depression, and systolic blood pressure (SBP) were recorded at rest and during treadmill walking (TW). The end point during TW was either AP or fatigue. Each pt was studied on 6 mornings over a period of 3 weeks. Each morning, studies were repeated at hourly intervals for 4 hours after 4 cummulative oral doses of each drug or matching PL capsules. In comparison to PL all 5 drugs reduced resting HR ($P<0.01$). Mean± SEM values for TW times in seconds to AP are shown:

	1C	2C	4C	8C
PL	168±15	169±20	174±17	180±20
P	212±36*	267±39**	331±46**	348±44**
Ox	245±15**	283±19**	336±52**	362±52**
Pra	206±28	267±53**	319±55**	352±62**
Tol	230±31*	369±58**	399±78**	402±65**
Met	241±31*	348±63**	353±52**	380±51**

1 C (Capsule) = 40 mg P or Ox, 100 mg Pra, 50 mg Tol or Met, or PL. * = $P<0.05$, ** = $P<0.01$ compared to PL.

In comparison to PL, all drugs at all doses significantly reduced HR, SBP, and ST depression during TW ($P<0.01$). Increase in TW time, reduction in HR, SBP, and ST segment depression after the 5 drugs were of equal magnitude. It is concluded that these drugs, irrespective of different ancillary pharmacological properties are equally effective in improving exercise tolerance and modifying circulatory responses during exercise induced angina.

CLINICAL ELECTROPHYSIOLOGIC EFFECTS OF TOCAINIDE

Jeffrey L. Anderson, MD; Jay W. Mason, MD; Roger A. Winkle, MD, FACC; Peter J. Meffin, PhD; Robert E. Fowles, MD; Flora Peters, RN; Donald C. Harrison, MD, FACC, Cardiology Division, Stanford Medical Center, Stanford, CA.

The electrophysiologic properties of tocainide, an orally effective primary amine analog of lidocaine, were evaluated by electrophysiologic studies in 12 patients before, during, and after a constant intravenous infusion of tocainide, 0.5 or 0.75 mg/kg/min, for 15 minutes. Peak plasma tocainide concentrations averaged 11.0±1.7 μg/ml (SEM), range 3.7 to 22.7. Wenckebach cycle length was unchanged. Results of electrophysiologic studies at 0 and 30 minutes included (values in msec):

Min	CSNRT	AERP*	AVNERP†	AVNFRP	RVERP†	WCL
0	371±51	258±14	346±22	464±21	298±14	449±30
30	378±37	241±9	324±20	450±26	275±11	454±26

* = $p<0.05$; † = $p<0.01$; CSNRT = corrected sinus node recovery time; AERP = atrial effective refractory period; AVNERP = AV nodal effective refractory period; AVNFRP = AV nodal functional refractory period; RVERP = right ventricular effective refractory period. WCL = Wenckebach cycle length.

AH, HV, QRS, QTc and RR intervals were measured every 5min between 0 and 30 min during sinus and atrial-paced rhythms and showed small changes (which were NS) for HV and QRS. Mild shortening of RR was significant ($p<.05$) at 15 min only. AH tended to increase slightly for spontaneous but not paced rhythm, becoming significant at 15 min only ($p<.05$). QTc decreased slightly for paced but not spontaneous rhythm. A progressive rise in mean arterial pressure occurred during drug infusion ($p<.01$). These results obtained at therapeutic plasma concentrations suggest qualitative similarities between the conduction system effects of tocainide and those published for lidocaine.

NORMALIZATION OF MYOCARDIAL ENERGY METABOLISM AND CARDIAC FUNCTION BY TREATMENT WITH PROPRANOLOL AND DIBUTYRYL cAMP DURING SHORT-TERM CIRCUMFLEX ARTERY OCCLUSION IN DOGS
Trenton B. Allison, PhD and James W. Holsinger, Jr., MD, PhD, VA Hospital, Newington, Connecticut.

The purpose of this study was to examine ways to normalize myocardial energy levels and cardiac function during acute ischemia. The circumflex artery was isolated in anesthetized, open-chest dogs and a silk suture placed around it. Baseline measurements of heart rate (HR), LVEDP, dP/dt/P and cardiac output (CO, ml/min/kg) were made. Five groups (N=6) were studied: Control (C); 20 min occlusion (OCC); Propranolol (P, 1 mg/kg, iv) given 10 min prior to OCC; Dibutyryl cAMP (0.5 mg/kg/min) begun 5 min after P and 5 min prior to OCC (P+DBcAMP) and DBcAMP begun 5 min before OCC. After 20 min, hemodynamics were recorded. A transmural core biopsy was obtained from the posterolateral wall of the LV, frozen in liquid N_2, separated into epicardium (EPI) and endocardium (ENDO) and ATP and phosphocreatine (PCr) extracted and analyzed. For hemodynamic data below, X = post OCC. [* = P<0.01 vs C].

		OCC		P		P+DBcAMP		DBcAMP	
	C	C	X	C	X	C	X	C	X
HR	149	153	151	148	111*	149	128*	145	170*
LVEDP	5.6	4.6	6.8*	5.6	12.9*	6.0	7.9*	6.0	7.4
dP/dt/P	35.4	33.0	32.8	31.4	27.6*	37.2	35.6	30.6	48.8*
CO	84.8	85.2	84.3	91.1	57.5*	80.1	81.1	78.8	122.6*

EPI and ENDO levels of ATP and PCr, μm/g dry wt±SE, shown below, reflect the energy status of the myocardium.

		C	OCC	P	P+DBcAMP	DBcAMP
ATP	EPI	28.1±0.4	18.2±0.8	24.9±1.6	27.7±1.5	21.1±0.9
	ENDO	22.1±1.0	10.7±1.1	19.0±1.8	22.1±1.8	16.4±1.2
PCr	EPI	42.2±1.6	11.1±0.6	31.6±3.4	46.5±3.4	12.3±1.9
	ENDO	32.4±1.2	6.5±0.4	16.3±1.0	22.1±1.7	7.7±1.3

These data indicate that DBcAMP can normalize cardiac function in the P treated acutely ischemic myocardium and enhance the protective effect of P on energy metabolism.

INCREASE IN FIBRILLATION THRESHOLD PRODUCED BY VERATRINE IN THE INFARCTED DOG HEART.
E.R. Arbel, M.D., A. Ellis, J. York, G. Glick, M.D., F.A.C.C., Cardiovascular Institute, Michael Reese Hospital, Chicago, Illinois.

The effect of veratrine infused intravenously (0.18 mg/kg) on the fibrillation threshold of the right, RVFT, (6 dogs) and left, LVFT, (5 dogs) ventricles was determined in anesthetized open chest dogs after permanent occlusion of the left anterior descending coronary artery. The RVFT was 43±9 mA during the control period and 40±7 mA after 45' of occlusion (p NS). It rose to 78±11 mA after veratrine (p <0.005) and was higher than the corresponding RVFT in 5 dogs subjected to coronary occlusion in which saline was infused instead of veratrine (30±4 mA, p <0.05). The LVFT decreased from a control value of 43±12 mA to 31±10 mA 45' after occlusion (p <0.005). It rose to 73±3 mA after veratrine (p <0.005), and this increase was unaffected by atropine and vagotomy. The duration of post defibrillation ventricular arrhythmia was 12±4 sec after occlusion and 2±0.7 sec after veratrine (p <0.02). The heart rate was 151±5 beats/min at control and 147±11 beats/min after occlusion (p NS). It decreased to 122±13 beats/min after veratrine (p <0.001). The mean arterial BP was 148±9 mm Hg at control and declined to 135±6 mm Hg after occlusion (p <0.05) and to 104±10 mm Hg after veratrine (p <0.01). The QT interval was 230±12 msec at control and did not change after occlusion (232±12 msec). It increased to 278±23 msec after veratrine (p <0.05). Thus, veratrine represents a new class of drugs that enhances electrical stability of the dog heart during acute myocardial infarction.

COMPARATIVE EFFICACY OF INTRAVENOUS DISOPYRAMIDE AND LIDOCAINE IN VENTRICULAR DYSRHYTHMIAS
Danilo Deano, MD; Steven Swiryn, MD: David Best, MD; Robert Highley, MD: Delon Wu, MD, FACC; Kenneth Rosen, MD, FACC, University of Illinois, Chicago, Illinois

Although it is known that intravenous disopyramide phosphate (DP) is antiarrhythmic, there is no reported data comparing this agent with other parenteral antiarrhythmic drugs. In this study, we administered DP and lidocaine (LID) to 27 patients (pts) with stable ventricular dysrhythmias: 19 with VPC's ≥124/hour (mean±SEM = 881±124) and 8 with repetitive or sustained ventricular tachycardia (VT). The drugs were given sequentially (initial drug chosen by randomization) with a mean interval of 6.5 hours between drugs. DP was given as follows: 2mg/kg over 15 min., followed by 2mg/kg over 45 min. and then 0.4mg/kg per hour. LID was administered as 1mg/kg bolus followed by 1mg/kg bolus 15 min. later. A LID drip at 4mg/min. was started following the first bolus. Termination of VT or greater than 50% suppression of VPC's for 12 hours was considered a successful response. Of 27 pts, 7 (26%) responded to DP alone, 3 (11%) responded to LID alone, 10 (37%) responded to both, and 7 (26%) responded to neither (total of 17 DP responders and 13 LID responders). Of 16 pts with ischemic heart disease, 11 responded to DP (69%) and 6 to LID (P<0.20). No electrocardiographic characteristics of VPC's or VT predicted drug response. Two pts had to discontinue DP because of nausea in one and heart failure in the other. Two pts had to discontinue LID because of severe CNS symptoms. In conclusion, both LID and DP were effective antiarrhythmic drugs for management of ventricular dysrhythmias with equivalent low incidence of serious toxicity. Although total numbers were small, DP seemed more efficacious particularly in pts with ischemic heart disease.

DEPRESSANT EFFECTS OF QUINIDINE GLUCONATE ON LEFT VENTRICULAR CONTRACTION AND RELAXATION IN CONSIOUS DOGS WITH VOLUME OVERLOAD
- Robert Engler, MD; Martin LeWinter, MD; Linda Van Nyhuis; Rodney Kaiser, MD, PhD; Joel Karliner, MD, FACC: VA Hospital, La Jolla, Ca. and Univ. of Ca., San Diego, Ca.

The effects of quinidine gluconate (Q) on left ventricular (LV) function in volume overload (VO) hypertrophy states are unknown. Therefore, we gave intravenous Q (10-12 mg/kg) to conscious dogs instrumented with atrial pacing wires, LV micromanometers and ultrasonic dimension gauges at one week and one month after creation of an aorta-caval fistula. Mean Q levels at time of study (5 minutes post infusion) were within therapeutic range. Without autonomic blockade (AB), heart rate (HR) increased by 16±3 (SE) bpm and LV end-diastolic pressure (EDP) fell by 5.5±.7 mm/Hg (both p<.005). The time constant for LV isovolumic pressure fall (T) fell from 18.9±1.8 to 15.6±.7 msec (p<.001). LV peak +dp/dt, dp/dt at developed pressure 40 (dp40), % shortening (%ΔD) and LV systolic pressure were unchanged. Mean Vcf increased from 1.61±.09 to 1.73±.11 circ/sec (p<.01). When Q was given during AB at a constant paced HR, LVEDP was unchanged and LV systolic pressure fell by 18.5±3.2 mmHg (p<.001). Peak (+) LV dp/dt decreased from 3022±131 to 2074±147 mmHg/sec (p<.01), and dp40 decreased from 2522±118 to 1781±141 (p<.001). Mean Vcf decreased from 1.52±.21 to 1.30±.19 circ/sec (p<.01) and %ΔD from 23.0±3.2 to 19.5±2.0% (p < .01). T increased from 20.2±1.4 to 25.8±1.6 msec (p<.02). Thus, combined AB and atrial pacing unmasked significant depressant effects of Q on LV ejection phase indices, isovolumic phase indices, and the rate of isovolumic pressure fall in dogs with chronic VO. We conclude that in the absence of autonomic blockade this depression was masked by augmented sympathetic tone.

REAPPRAISAL OF THE MECHANISM OF ACTION OF ANTIARRHYTHMIC DRUGS ON ISCHEMIC REENTRANT VENTRICULAR ARRHYTHMIAS

Nabil El-Sherif, MD; Ralph Lazzara, MD, V. A. Hospital and Univ. of Miami, Miami, Fla.

We conducted an in vivo-in vitro correlative study of the effect of lidocaine (L), diphenylhydantoin (D), practalol (P) and verapamil (V) on reentrant ventricular arrhythmias (RVA) in dogs 3-5 days following ligation of the anterior descending coronary artery. The in vivo study analyzed direct recordings of the electrical activity of the reentrant pathways (RP) from the epicardial surface of the infarction zone (IZ). The in vitro study utilized strips of epicardial muscle from the IZ and a standard microelectrode technique. Both L and D were found to selectively prolong refractoriness and depress conduction in ischemic muscle forming part of the RP. This effect was directly related to their antiarrhythmic action which resulted from complete block in the RP. L and D markedly depressed hypopolarized ischemic cells in vitro. Thic action was qualitatively similar to that of tetrodotoxin. P depressed conduction in the RP in vivo but had no membrane effect in vitro. Its action was ascribed to abolition of the permissive effect of tonic adrenergic impulses on conduction in the RP. Contrary to the effect of L, D and P, V had a slight enhancing effect on conduction in the RP and slightly improved depressed ischemic cells in vitro. This could also result in a moderate antiarrhythmic effect especially on RVA initiated by premature beats. The in vitro study suggests that ischemia results in depression of the fast Na channel, that L and D act by further depression of this channel while V may slightly improve the Na channel probably by a sparing effect on endogenous energy resources. In summary, this study provides a new insight into the mechanism of action of antiarrhythmic agents in ischemic RVA.

VERAPAMIL EFFECTS ON BLOOD SUPERFUSED PURKINJE FIBERS: EVIDENCE FOR DIRECT AND CATECHOLAMINE-MEDIATED ACTIONS.

Peter Danilo, Jr., PhD; Allan J. Hordof, MD; Ellise S. Delphin, MD; Michael R. Rosen, MD, FACC. Columbia University, New York, NY.

Verapamil (V) is an effective antiarrhythmic agent which exerts its major cellular electrophysiologic effects on slow response action potentials (AP). We determined whether doses of V that modify the electrophysiologic properties of markedly depressed Purkinje fibers (PF) having AP characteristic of the slow response exert a significant effect on the body surface ECG. We superfused PF having either depressed or normal AP with blood from anesthetized donor dogs. We administered V intravenously to the donors and recorded its effects on donor ECG and arterial blood pressure and on the AP of the isolated PF. V, 50-400 µg/kg induced a dose-dependent increase in P wave duration and P-R interval. At V > 400 µg/kg complete heart block occurred. In PF with normal AP V, 50-400 µg/kg induced minimal dose-dependent decreases in AP amplitude, maximum diastolic potential (MDP) and AP duration. V exerted a biphasic effect on depressed AP. V, 50-100 µg/kg often increased MDP, AP amplitude, and upstroke velocity of phase 0. This effect was associated with an increase in the donor heart rate and a decrease in P-R interval. These effects on the AP, heart rate and P-R interval were blocked by pretreatment with propranolol, 0.5 mg/kg IV. In the presence of propranolol V depressed AP amplitude and phase 0 upstroke velocity. V 200-400 µg/kg invariably depressed or abolished the AP of depressed fibers. In summary, normal PF AP are affected only slightly by doses of V which markedly depress or block A-V conduction. In contrast, the depressed or slow response AP is further depressed by doses of V which slow but do not block A-V conduction. V apparently also can induce catecholamine release, which may enhance the AP of depressed fibers.

ROLE OF CYCLIC ADENOSINE MONOPHOSPHATE IN REGULATION OF VULNERABILITY TO VENTRICULAR FIBRILLATION IN RAT HEART.

Wilhelm F. Lubbe, MD; Lionel H. Opie, MD, FACC. University of Cape Town, South Africa.

Catecholamine-mediated mechanisms are important in the genesis of ventricular fibrillation (VF) in acute myocardial ischemia. Hence we have explored the relationship between cyclic adenosine monophosphate (cAMP), the second messenger of β-adrenergic agonist activity, and the ventricular fibrillation threshold (VFT) of the isolated perfused rat heart. Increased intracellular cAMP was achieved by β-stimulation, by phosphodiesterase inhibition or by addition to the perfusate of dibutyryl cAMP (DB cAMP) which is thought to penetrate the cell membrane in contrast to sodium cAMP which penetrates poorly. Epinephrine (100 nmol to 1 µmol/l) caused a concentration-related increase in tissue cAMP and a biphasic response curve of VFT; the curve was shifted to the left by theophylline and to the right by atenolol, a β-1 selective adrenergic blocking agent. DB cAMP (30 - 500 µmol/l) caused a concentration-related fall in VFT without alteration in tissue adenosine triphosphate or creatine phosphate; theophylline (1.0 mmol/l) shifted this response curve to the left but atenolol had no effect. Sodium cAMP decreased VFT only in the presence of theophylline. The decrease in VFT induced by coronary artery ligation was also accompanied by an increased tissue cAMP in the ischemic zone. The VFT in coronary-ligated hearts was further decreased by theophylline which further increased cAMP in the ischemic zone.

We conclude that an increased tissue cAMP induced by β-1 stimulation, theophylline, dibutyryl cAMP, or ischemia is accompanied by increased vulnerability to VF. We postulate that cAMP is an important regulator of ventricular vulnerability.

IMPLICATION OF cAMP AND CALCIUM AS MEDIATORS OF AUTOMATICITY INDUCED IN WORKING MYOCARDIUM

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Transient after-depolarizations (AD) and triggerable automaticity (A) were induced in normally non-automatic myocardial cells. Canine ventricular preparations were superfused with a modified Tyrode solution (K=4mM/L; Ca=1.4mM/L) and transmembrane potentials recorded with conventional methods. AD were consistently induced by β adrenergic agonists (norepinephrine$\geq 5\times10^{-7}$M; isoproterenol$\geq 10^{-9}$M). The amplitudes of AD were increased and A enhanced by the addition of various phosphodiesterase inhibitors (papaverine, 2.5×10^{-5}M; 3-isobutyl-1-methyl xanthine, 5×10^{-5}M) and dibutyryl cAMP (0.1mM). At higher concentrations, slow diastolic depolarization like that of normally automatic cells was sometimes observed, especially in partially-depolarized cells. The amplitudes of AD were depressed by β adrenergic blockade (practolol 4×10^{-6}M) and hypoxia. Amplitudes of AD varied with temperature with a Q10>2. The amplitudes of AD were directly and strongly related to the external concentration of Ca^{++}(0.7-2.8mM/L) and directly but weakly related to external Na^{+}(70-140mM/L). AD were strongly suppressed by D-600(2×10^{-6}M), an inhibitor of inward Ca^{++}current and only slightly affected by tetrodotoxin(1.5×10^{-6}M). Acetylcholine(10^{-8}M) depressed AD. Thus, A may be induced in normally non-automatic cells by factors known to increase the level of cAMP and abolished by factors which decrease cAMP or increase cGMP. AD depend strongly on external Ca^{++} and are attenuated greatly by blockers of inward Ca^{++} current. The data indicate that AD and induced A are the result of diastolic inward current, mainly Ca^{++}, mediated by cAMP.

WEDNESDAY, MARCH 8, 1978
PM
PEDIATRIC CARDIOLOGY—II
2:00 to 3:30

LABORATORY EVALUATION AND SELECTION FOR SURGERY OF PATIENTS WITH PULMONARY ATRESIA AND VENTRICULAR SEPTAL DEFECT

Douglas D. Mair, MD, FACC; Richard E. Fulton, MD; George D. Davis, MD; Donald J. Hagler, MD, FACC; James B. Seward, MD; Abdul J. Tajik, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minn.

During the past 10 years, 180 patients with pulmonary atresia and ventricular septal defect have been evaluated in our laboratory. The suitability of these patients for definitive or palliative operation is primarily dependent on the anatomy of the pulmonary blood supply. For definitive operation to be successful, our experience has shown that the following criteria must be met: (1) at least one true pulmonary artery must be present, (2) the pulmonary artery(s) must supply lung parenchyma at least equal to the volume of one normal-sized lung, and (3) the total area of the pulmonary artery(s) at the hilum must be equal to at least ½ the area of the descending aorta at the diaphragm. Special angiographic techniques such as (1) selective injection of systemic collateral vessels, (2) subtraction of radiographic images, and (3) pulmonary venous wedge angiography are often necessary to establish the presence and distribution of true pulmonary arteries. Using these techniques, we found 114 patients (63%) with two confluent true pulmonary arteries and 36 (20%) with two nonconfluent or a single true pulmonary artery. In patients with pulmonary arteries that were too hypoplastic to permit definitive repair, increasing the flow through these vessels by means of a shunt or a right ventricular-to-main pulmonary artery pericardial patch graft provided excellent palliation and, in several instances, stimulated the hypoplastic arteries to grow and become adequate for second-stage definitive operation.

COMPARATIVE HEMODYNAMIC EFFECTS OF NITROPRUSSIDE, PRAZOSIN AND HYDRALAZINE IN REFRACTORY HEART FAILURE

Jawahar Mehta,M.D., Marie Iacona,M.D., Carl J. Pepine,M.D. F.A.C.C., C. Richard Conti,M.D.,F.A.C.C., Cardiovascular Division, University of Florida and V.A. Hospital, Gainesville, Florida

In order to evaluate optimum oral vasodilator therapy, hemodynamic effects of prazosin 4mg(PRZ) and hydralazine 100mg(HYD) were observed in 11 patients(pts) with refractory heart failure and compared to IV nitroprusside(NP) in same pts. Left ventricular(LV) filling pressure(FP) fell 44%($p<.01$) with NP, 32% ($p<.01$) with PRZ and 9% (p-NS) with HYD(p-NP vs PRZ<.05, NP vs HYD<.01). Cardiac index(CI) increased 41%($p<.01$) with NP, 32%($p<.01$) with PRZ and 43%($p<.01$) with HYD(p-NS both NP vs PRZ & NP vs HYD). Heart rate was unchanged with all three, arterial pressure declined slightly with NP and PRZ but not with HYD. LV stroke work index(SWI) increased from 21.4±2.7 to 30.0±2.1 $g\text{-}m/m^2$($p<.01$) with NP, from 22.4±2.7 to 26.6±1.9 $g\text{-}m/m^2$($p<.01$) with PRZ and from 22.0±2.1 to 33.9±2.3 $g\text{-}m/m^2$($p<.01$) with HYD(p-NP vs PRZ<.05, NP vs HYD-NS). Systemic vascular resistance decreased 36% with NP, 30% with PRZ and 33% with HYD(p-NP vs PRZ-NS, NP vs HYD-NS). Pulmonary resistance fell 37%, 31% & 17% with NP, PRZ and HYD respectively(p-NP vs PRZ-NS, NP vs HYD<.01). Hemodynamic effects of PRZ peaked at 1 hour and persisted for 6 hours, whereas those of HYD peaked at 3 and persisted for 8 hours after administration. These data show that NP and PRZ have qualitatively similar actions,though NP results in slightly greater fall in LVFP and greater increase in LVSWI. This observation indicates a balanced action of PRZ on preload and afterload like NP. HYD produces a greater increase in CI and LVSWI with no change in LVFP suggesting predominantly afterload reduction or direct inotropic action. Thus, ambulatory pts with a low forward CI may benefit from HYD, whereas pts with a low CI and high LVFP might best be treated with PRZ.

THE DIFFERENTIATION OF FUNCTIONAL FROM ORGANIC PULMONARY ATRESIA: THE ROLE OF AORTOGRAPHY.

Robert M. Freedom, M.D, F.A.C.C., J.A.G. Culham, M.D., Peter M. Olley, M.D., F.A.C.C., C.A.F. Moes, M.D., and Richard D. Rowe, M.D. The Hospital for Sick Children, Toronto, Ontario, Canada.

Among certain critically ill neonates with severe tricuspid regurgitation, including those with Ebstein's anomaly of the tricuspid valve, tricuspid valve dysplasia,transient tricuspid regurgitation of the newborn, Uhl's anomaly, hypoplasia of the right ventricle(RV), etc., selective right ventriculography may not distinguish between functional or organic pulmonary atresia. With a normal pulmonary valve and infundibulum, functional obstruction in such patients(pts.) results from a combination of massive tricuspid insufficiency and an elevated perinatal pulmonary vascular resistance. This differentiation between functional and organic pulmonary atresia is essential because of the therapeutic implications.

Thirty-three such neonates with severe tricuspid regurgitation were studied at cardiac catheterization from January, 1974 through August, 1977 in whom standard hemodynamic measurements and right ventriculograms could not distinguish between functional and organic pulmonary atresia. Retrograde aortography, in the presence of a patent ductus arteriosus, provided excellent visualization of the pulmonary root and valve in these cases, and without exception, pulmonary regurgitation across the valve was observed in pts. with functional pulmonary atresia. Usually, the regurgitated contrast material was significant enough to opacify both right ventricle and right atrium. In addition, among the pts. with functional pulmonary atresia, the pulmonary root and valve appeared wider and more patulous than the patient with organic pulmonary atresia. If there was evidence of ductal narrowing, administration of an E-type Prostaglandin prior to aortography both improved systemic oxygenation and allowed better visualization of the pulmonary root. Although trivial pulmonary regurgitation may rarely be visualized on aortography among those pts. with critical organic pulmonary stenosis, aortography still provides a useful way of differentiating organic from functional pulmonary atresia among pts. with severe tricuspid regurgitation.

ANATOMIC TYPES OF SUBPULMONARY STENOSIS IN D-TRANSPOSITION OF THE GREAT ARTERIES BY ECHO AND ANGIOGRAPHY

Roberta G. Williams, MD; Kenneth E. Fellows, MD; Aldo R. Castaneda, MD, FACC, Childrens Hospital Medical Center, Boston, Massachusetts

Subpulmonary stenosis(SPS)in D-transposition of the great arteries(TGA)may be caused by: dynamic septal mitral apposition with or without septal hypertrophy(types A&B), anomalous endocardial cushion tissue(type C), posterior deviation of the parietal band(type D), or subpulmonary conus muscle(type E). Echo and angiographic observations were compared in 23 patients with TGA and SPS and related to findings at surgery. Nine patients with intact ventricular septum(IVS)had SPS with>50 mmHg gradient; 1 was type A, 3 type B and 5 type C. One patient with type A had partial septal resection and 1 with type B had myotomy with partial relief of suprasystemic pressures. Three patients with type C had resection of the subpulmonary area with continued moderate postoperative gradient; in 1 patient, no resection was attempted because the mitral valve was densely adherent to the ventricular septum. Fourteen patients had a ventricular septal defect and SPS; of these, 3 had type C, 9 type D and 2 type E. Postoperative hemodynamic data is not yet available in these patients. Echo and angiographic descriptions coincided in 21/23 patients but were discrepant in 1 patient with severe type D and another with an anomalously placed papillary muscle in addition to a fibrous ridge. Septal thickness, anatomy of the mitral apparatus and details of mitral leaflet motion are better described by ultrasound, while angiography is superior in defining fibromuscular ridges and subpulmonary conus. A combination of both techniques offers the best predication of the ability to surgically relieve SPS in TGA. This is particularly important because the transpulmonary approach offers a suboptimal view of the subpulmonary area at the time of surgical repair.

INFANT RATS RAISED IN HYPOXIA: A PATHOPHYSIOLOGIC STUDY OF REVERSIBLE PULMONARY VASCULAR DISEASE (PVD)

Marlene Rabinovitch, MD; Walter J. Gamble, MD; Alexander S. Nadas, MD, FACC; Lynne Reid, MD, Children's Hospital Medical Center, Boston, Massachusetts

Thirteen infant rats (Charles River-CD) were raised in hypoxia (a hypobaric chamber with air at 380mmHg) from day 8 to 45 of life to assess the reversibility of PVD. A group of 6 was studied immediately after hypoxic exposure (H-rats) and another of 7 was allowed 1 month to recover in room air (H-R rats). Each group was matched in age and number with nonhypoxic controls (C-rats). Indwelling pulmonary artery (PA) and aortic (Ao) catheters were placed in H, H-R and C-rats so that PA and Ao pressures (P) could be measured the following day with the rats unanesthetized. All animals were sacrificed on the day of measurement. Right ventricular hypertrophy (RVH) was assessed by the ratio of left to right ventricular weights (LV/RV). PVD was evaluated after injecting the PA tree with barium-gelatin and the bronchial tree with formalin, by 3 morphometric criteria (i) extension of muscle into small vessels (EMSV); (ii) percentage wall thickness (%WT); and (iii) alveolar arterial ratio (A/A). Measurements in the 2 C-rat groups were similar. Mean AoP (AOP) was not significantly different in H, H-R or C-rats; mean PAP was elevated to 50% AOP in H-rats, fell to 25% AOP in H-R rats but was still 15% AOP in C-rats ($p=<.02$-$.001$). Comparing morphologic criteria of PVD in H and H-R rats there was regression of EMSV ($p=<0.02$) %WT ($p=<.1$) and A/A ($p=<.05$). All values were still higher than those of C-rats; (p for EMSV=<0.1, %WT=<0.2 and A/A=<0.C01). In conclusion, infant rats raised for a month in hypoxia develop hemodynamic and morphologic evidence of severe PVD but after an equivalent recovery period the PAP falls toward normal in association with the regression of muscle and the apparent proliferation of new arteries in the peripheral pulmonary vascular bed.

WEDNESDAY, MARCH 8, 1978
PM
VASODILATOR THERAPY
4:00 to 5:15

EPHEDRINE-NITROPRUSSIDE COMBINATION IN CONGESTIVE HEART FAILURE

J. A. Franciosa, MD, FACC; J. N. Cohn, MD, FACC, University of Minnesota and Veterans Administration Hospitals, Minneapolis, Minnesota.

Combination of nitroprusside (NP) and intravenous inotropic drugs is more effective than either agent alone in some patients with congestive heart failure (CHF). Oral vasodilators can mimic NP, but potent oral inotropic agents are lacking. Ephedrine (E) is an oral sympathomimetic inotropic agent. We observed hemodynamic effects of NP, E (50 mg orally), and E+NP in 7 patients with CHF. Heart rate of 86.1 ± 7.1 (SEM) beats/min rose 5.9 ± 1.7 beats/min after E ($p<0.02$) and was unchanged by NP or E+NP. Mean intra-arterial pressure of 84.6 ± 3.4 mm Hg rose slightly after E (5.3 ± 3.4 mm Hg), and fell after NP (-17 ± 1.8 mm Hg) and E+NP (-13.8 ± 2.5 mm Hg), both $p<0.01$. Pulmonary wedge pressure increased slightly from 29.6 ± 2.9 to 31.6 ± 3.3 mm Hg after E, and fell after NP and E+NP (-8.7 ± 1.0 mm Hg and -8.8 ± 0.9 mm Hg respectively, both $p<0.001$). Control cardiac output (CO - by thermodilution) averaged 3.76 ± 0.42 L/min and increased with all regimens; E = +1.20 ± 0.46 L/min, $p<0.05$; NP = +1.55 ± 0.42 L/min, $p<0.02$; E+NP = +2.40 ± 0.49 L/min, $p<0.01$. The increase in CO was similar for NP and E, but significantly greater for E+NP compared to NP or E alone ($p<0.05$). Systemic vascular resistance was unchanged by E but fell significantly after NP and E+NP. The data suggest that a single dose of E is an orally effective inotropic agent in CHF, especially when combined with a vasodilator. Evaluation of chronic use of E in CHF is warranted, particularly in regard to possible tachyphylaxis.

DISTAL AORTIC PRESSURE FOLLOWING BALLOON OCCLUSION OF MODERATE COARCTATION

Donald A. Girod, MD, FACC; Roger A. Hurwitz, MD, FACC; Randall L. Caldwell, MD; Edmund A. Franken, ME; Indiana University Hospital, Indianapolis, Indiana

Paraplegia following coarctation (Co) repair occurs in 0.5 per cent of cases. Patients (pts) with moderate (less severe) Co frequently have poor development of collateral arteries, potentially complicating surgery. Such pts frequently have significant hypertension, thus making surgery desirable. In an attempt to aid in planning possible surgery, 9 pts with clinical signs of moderate Co and 4 patients with signs of severe (usual) Co underwent balloon occlusion of the Co and measurement of the distal aortic pressure, simulating aortic clamping at surgery. Measurement of gradients across the Co and angiographic evaluation of collaterals was also done. Among 9 pts with moderate Co, the Co systolic gradient was 23-36 mm Hg. During balloon occlusion, the distal aortic systolic pressure fell from (range) 67-102 to 33-56. Among 4 pts with severe Co, the systolic gradient was 49-90. During balloon occlusion, the distal aortic systolic pressure fell from 76-91 to 55-75. Based on the drop of aortic pressure below 50 mm Hg, surgery has been recommended with pump-oxygenator standby in all 9 pts with moderate Co. Five pts with moderate Co have undergone surgery with aortic clamping distal aortic pressure fell to 30, 30, and 35 in 3 pts. Coarctectomy with end-to-end anastomosis was performed utilizing atrio-femoral and femoral-femoral bypass in two cases, and subclavian artery to descending aorta graft in the third. In 2 pts, the distal aortic pressure did not fall and routine repair was done. Four pts with moderate Co await surgery. Four pts with severe Co were treated routinely. Balloon occlusion of Co may reveal inadequacy of collateral arteries and aids in planning of surgery.

HEMODYNAMIC EFFECTS OF CONVERTING ENZYME INHIBITOR IN CONGESTIVE HEART FAILURE

C. Curtiss, MD; T. Vrobel, MD; J. A. Franciosa, MD, FACC; J. N. Cohn, MD, FACC, University of Minnesota and Veterans Administration Hospitals, Minneapolis, Minnesota.

Reduction of elevated systemic vascular resistance (SVR) by vasodilators improves hemodynamics in congestive heart failure (CHF). Because the increased SVR might be dependent in part upon plasma renin activity (PRA), we gave converting enzyme inhibitor (CEI) (SQ 20881) to 10 patients with CHF and observed hemodynamic responses at peak effect 10-30 min after intravenous boluses of 0.25 - 2.00 mg/kg. Heart rate was 80.8 ± 3.4 (SEM) beats/min before and 76.0 ± 3.1 beats/min after CEI ($p<0.05$). Following CEI mean intra-arterial pressure fell from 86.2 ± 5.4 to 73.2 ± 5.7 mm Hg and cardiac output (by thermodilution) rose from 4.04 ± 0.28 to 4.83 ± 0.37 L/min resulting in a drop in SVR from 1594 ± 206 to 1163 ± 177 dynes-sec-cm^{-5} (all $p<0.001$). Right atrial pressure and pulmonary wedge pressure (by Swan-Ganz catheter) both fell after CEI, the former from 12.3 ± 1.3 to 9.0 ± 1.1 mm Hg, $p<0.001$, and the latter from 25.9 ± 1.9 to 20.5 ± 1.8 mm Hg, $p<0.01$. Control PRA averaged 10.3 ± 4.1 ng/ml/hr and rose to 42.8 ± 19.5 ng/ml/hr after CEI ($p<0.01$ >0.05). The fall in SVR after CEI averaged 30.6 ± 4.3% and correlated with the control PRA ($r = 0.825$, $p<0.01$). Good responders (fall in SVR $\geq$ 33%) had higher control PRA (15.5 ± 6.8 ng/ml/hr) than poor responders (3.9 ± 0.6 ng/ml/hr), $p<0.02$. The data show that CEI is an effective vasodilator in CHF and suggest that the renin-angiotensin system contributes importantly to the high SVR in CHF.

PHYSIOLOGIC BASIS FOR AFTERLOAD REDUCTION FOLLOWING MITRAL VALVE REPLACEMENT

J. A. Mantle, MD, FACC; W. P. Hood, Jr., MD, FACC, N. T. Kouchoukos, MD, FACC; R. B. Karp, MD, FACC; D. Zisserman, Ph.D., and C. E. Rackley, MD, FACC. University of Ala. Medical Center, Birmingham, Alabama.

To investigate the cause of low cardiac output following valve replacement for mitral incompetence, the changes in systolic wall stress (σ) that occurred post-op were compared in 8 patients (pts). The σ was calculated for a modified Laplace model that accounts for left ventricular (LV) wall thickness as well as LV pressure and chamber radius. The pre-op σ was calculated from biplane cineangiograms and LV pressure. The post-op σ was calculated from cardiac index (CI), aortic and left atrial pressures and heart rate with the end-diastolic volume and mass held constant. Four pts developed a low CI post-op (low CI group) of 1.4±.2 vs 2.2±.2 L/min/m^2 pre-op ($p<.05$). The post-op CI in the remaining 4 pts was unchanged at 2.7±.1 (normal CI group). The pre-op LV volumes, ejection fraction, % regurgitant flow, CI, pressures and σ were similar for both groups. Post-op, the low CI group developed a 95% increase in σ from 346±27 to 675±52 kilodynes/cm^2 vs a 27% increase from 446±68 to 568±65 for the normal CI group. The marked increase in σ for the low CI group resulted from elimination of the regurgitant flow plus a 50% increase in the systolic pressure to 153±9 mm Hg. With reversal of the hypertensive response by vasodilators, the CI returned to 2.2±.1.

Summary: In pts having valve replacement for mitral incompetence: 1) Elimination of regurgitant flow plus a mild increase in systolic pressure can produce a significant increase in systolic wall stress and reduce cardiac output. 2) Reduction of systolic wall stress by vasodilators can help to restore cardiac performance.

DOSE DEPENDENT REDUCTION IN RIGHT AND LEFT VENTRICULAR FILLING PRESSURES WITH HYDRALAZINE

Milton Packer, MD; Jose Meller, MD, FACC; Richard Gorlin, MD, FACC; Louis Teichholz, MD, FACC; Michael Herman, MD, FACC; Mount Sinai Hospital, New York, New York.

Hydralazine (H) increases (↑) cardiac index (CI) in patients (pts) with refractory heart failure (RHF) but the effects on right and left ventricular filling pressures (VFP) are disputed. To clarify this, single oral doses of 50, 75 and 100 mg H were administered at 24 hr intervals to each of 10 pts with RHF. Thermodilution CI (L/min/M^2), mean arterial (MAP), pulmonary wedge (PWP) and mean right atrial pressures (RAP) (mm Hg) were determined every 30 min for 8 hrs. Results (mean Δ ± SEM for 10 pts):

Dose	ΔCI	ΔMAP	ΔPWP	ΔRAP
50 mg	↑0.11±.15	↓6.4±1.2**	↓0.3±1.2	↑1.1±0.9
75 mg	↑0.59±.13**	↓8.2±1.6**	↓2.8±1.3	↓1.1±0.8
100 mg	↑1.01±.14**	↓11.5±2.2**	↓5.7±1.2**	↓2.9±0.9*

VFP (PWP and RAP) differed significantly from baseline at $p<.01$ (**) and $p<.05$ (*) respectively only with 100 mg doses. Doses of 75 mg ↑ CI and decreased (↓) MAP without significant changes in VFP. Changes in CI and VFP with 100 mg were markedly ($p<.01$) greater than with 75 mg doses, whereas the additional ↓ in MAP was minimal ($p>.10$). Responses in ischemic (4 pts) and nonischemic cardiomyopathies (6 pts) were similar. Individually, ↓ in PWP were highly correlated with changes in both RAP ($r=0.86$) and CI ($r=-0.87$). After institution of maintenance H therapy, 5 of the 6 pts who had demonstrated ↓ in PWP≥6 and ↓ in RAP≥3 with 100 mg doses experienced a brisk diuresis (>1000 cc in 8 hrs) with rapid clinical improvement. No enhanced diuresis was observed in any of the 4 pts who had demonstrated smaller ↓ in VFP with 100 mg. In conclusion, the use of 100 mg doses of H results in clinically significant ↓ in right and left VFP not achieved with smaller doses with little additional hypotensive risk.

ADRENERGIC REGULATION OF VENOUS CIRCULATION

David L. Rutlen, MD; Edward W. Supple; Wm. John Powell, Jr., MD, FACC; Mass. General Hospital, Boston, Mass.

Prior studies have demonstrated opposite effects of the same adrenergic agent on the venous circulation; in particular, isoproterenol has been demonstrated to cause dilatation in isolated veins but a displacement of intravascular volume consistent with venoconstriction in intact animals. The present study was undertaken to clarify the adrenergic regulation of systemic capacitance. Twenty-four dogs (20-22 kg) were anesthetized with chloralose and urethane, vagectomized, ganglionically blocked and placed on total cardiopulmonary bypass at 1.5 L/min. Isoproterenol (ISO) 6 µg/min and norepinephrine (NE) 30 µg/min were infused for 10-24 mins. Changes were noted in pump reservoir volume with central venous pressure (CVP) set at 3, 8 or 13 cm H_2O. ISO caused a loss of 20-150 (mean 80±30) mls from the dogs ($p<.05$) and NE, a loss of 190-290 (mean 240±30) mls ($p<.05$). Selective blockade with either phenoxybenzamine or propranolol and double blockade with both revealed that ISO induced volume changes were mediated entirely through beta adrenergic receptor stimulation whereas NE induced volume changes were mediated through both alpha and beta stimulation. After the hepatic and mesenteric vasculature was ligated in 2 animals, no changes in reservoir volume were noted with ISO or NE. In the animals without mesenteric vascular ligation ISO and NE each caused a decrease of 7±3 ($p<.05$) cm H_2O in splenic venous pressure from a mean of 25±4 cm H_2O for ISO and a mean of 27±1 cm H_2O for NE. In 2 of these animals, hepatic venous return was continuously monitored; with ISO or NE hepatic flow increased while the pressure gradient from splenic to hepatic vein decreased indicating a fall in resistance to portal outflow. Thus, ISO entirely, and NE in part, cause decreases in venous capacity by beta adrenergic relaxation of a portion of the venous circulation distal to the splenic vein.

THURSDAY, MARCH 9, 1978
AM
SURGERY FOR VALVULAR AND CONGENITAL HEART DISEASE
8:30 to 12:00

LONG-TERM PROGNOSIS AND SYMPTOMATIC STATUS OF PATIENTS AFTER OPERATION FOR IHSS

Barry J. Maron, MD; Walter H. Merrill, MD; Paul A. Freier, BA; Stephen E. Epstein, MD, FACC; Andrew G. Morrow, MD, NHLBI, Bethesda, Md.

Long-term postoperative status of 124 consecutive pts who underwent septal myotomy-myectomy for idiopathic hypertrophic subaortic stenosis (IHSS) from 1960-1975 were reviewed. Operation was performed because of severe symptoms refractory to medical therapy. Postop the large majority of pts reported distinct symptomatic improvement and virtually all manifested marked reduction in LV outflow gradient at rest. However, operative mortality was 8% and 12% of pts had persistent, or subsequently developed, recurrent severe functional limitation. In addition, late cardiac death still occurred despite abolition of gradient; the annual mortality rate following operation was 1.8%. Of the 11 late postop cardiac deaths, 6 were sudden and 5 were due to progressive congestive heart failure. Pts who were long-term survivors and those who died late postop did not differ with regard to age at operation or pre- or postop clinical, ECG or hemodynamic findings. However, 9 of the 11 (82%) pts with late death had complicating associated medical problems (AF, pulmonary or coronary disease, obesity) as opposed to only 43% of survivors ($p<0.05$). In conclusion, the large majority of pts experience long-term symptomatic benefits after septal myotomy-myectomy, confirming our belief that operation should be offered to pts with IHSS who have severe symptoms which respond inadequately to medical therapy. However, 20% of pts either died at operation or experienced no long-lasting symptomatic improvement. Since in some pts symptoms may progress and death occurs despite relief of obstruction, it appears that a subgroup of pts with IHSS exists in which the major long-term prognostic determinant is the cardiomyopathic component of the disease.

TREATMENT OF AORTIC ARCH ANEURYSM: A TWENTY YEAR EXPERIENCE

E. Stanley Crawford, MD, FACC; Raul Garcia-Rinaldi, MD; Douglas J. Milfeld, MD*

Aneurysms of the aortic arch involving the origins of the great vessels are rare. Replacement requiring perfusion techniques and myocardial protection during operation is thought to be associated with a high mortality rate. In fact, some have felt that the mortality is so high as to prohibit this form of therapy. This presentation is concerned with 20 patients treated during the past 20 years for aneurysms involving one or more of the great vessels arising from the aortic arch employing techniques available at the time of therapy. The entire arch including origin of the three major vessels were involved in 5 patients, two major vessels were involved in 6, and one vessel in 9 patients. Perfusion (cerebral) techniques were employed in 9 of the former 11 patients with survival in 9 (82%) but not in the latter 9 with survival in all cases. These results would appear to justify surgical treatment of these lesions. It is obvious that improvement would result both from additional experience and the application of newer methods of perfusion and cerebral protection because all patients treated during the past two years have survived.

*From the Cora and Webb Mading Department of Surgery, Baylor College of Medicine, and The Methodist Hospital, Houston, Texas

LONG TERM HEMODYNAMIC BEHAVIOUR OF THE IONESCU SHILEY PERICARDIAL XENOGRAFT HEART VALVE

Anand P. Tandon, MD, Donald R. Smith, MD, Marian I. Ionescu, MD. The General Infirmary, Leeds, England.

Since March 1971, 336 patients had heart valve replacement with pericardial xenografts. Of these, 69 had hemodynamic studies. Thirty-six patients with aortic replacement (AR) were investigated at a mean interval of 41.2 (range 22-59) months postop. The results showed significant increase in cardiac output ($p < 0.05$) and reduction in pulmonary wedge and LVED pressures ($p < 0.05$ and $p < 0.001$). Mean peak systolic gradients were 8.3 at rest and 12.3 mm Hg on exercise with the smallest xenograft (19 mm); and 0 and 1 mm Hg respectively with the largest one (27 mm). Calculated xenograft surface area (XSA) varied from 1.1 to 2.1 cm^2 at rest and 1.3 to 2.4 cm^2 on exercise. Twenty-nine patients with mitral replacement (MR) had hemodynamic studies at a mean interval of 40.2 (range 24-59) months postop. The results showed significant improvement in pulmonary artery and wedge pressures ($p < 0.001$ rest and $p < 0.01$ exercise). Mean diastolic gradients were 6 at rest and 15 mm Hg on exercise. Mean XSA was 2.0 and 2.3 cm^2 respectively. In 3 patients with tricuspid replacement the mean diastolic gradient was 2 to 4 mm Hg.

Thirteen patients with AR and six with MR had one preop and two postop sequential studies at approx. 1 and 4 years. No hemodynamic changes were noted between the two postop investigations.

The pericardial xenograft has shown very good hemodynamic performance even in patients with small aortic valves and the function of the xenografts was maintained up to 59 months postop.

HEMODYNAMIC EVALUATION OF THE IONESCU-SHILEY BOVINE HETEROGRAFT VALVE

Joel Strom, MD; Ronald M. Becker, MD; William Frishman, MD, FACC; Carlos Salazar, MD; Yasu Oka, MD; Gerald Bassell, MD, Yen Tse Lin, MD; Robert W. M. Frater, MD, FACC, Albert Einstein College of Medicine, Bronx, N. Y.

The intra-operative hemodynamic performance of the Ionescu-Shiley bovine pericardial heterograft valve was assessed in 28 patients who received 30 aortic and mitral prosthetic valves (AV and MV). Left atrial, left ventricular, and ascending aortic pressures were recorded while dye-dilution cardiac outputs were obtained simultaneously. The transvalvular gradients (grad) and cardiac outputs were used to estimate the effective orifice areas according to the Gorlin equation. The range of cardiac outputs was 1.50-6.56 L/min, mean 3.95 L/min.

Results for AV replacement:

AV Size	No.	Grad	Areas	Mean Area
21 mm	5	10.6-37.3 mmHg	0.6-1.3 cm^2	.97 cm^2
23 mm	10	3.8-20.3 mmHg	1.0-1.9 cm^2	1.4 cm^2
25 mm	4	3.2-13.3 mmHg	1.5-2.1 cm^2	1.8 cm^2
27 mm	1	3.4 mmHg	4.1 cm^2	4.1 cm^2

Results for MV replacement:

MV Size	No.	Grad	Areas	Mean Area
25 mm	1	15.3 mmHg	1.3 cm^2	1.30 cm^2
27 mm	5	2.7-13.7 mmHg	0.7-3.0 cm^2	1.53 cm^2
29 mm	4	7.2-13.0 mmHg	0.9-1.7 cm^2	1.29 cm^2

The Ionescu valve suffers from the same difficulties as other available prostheses, i.e., small effective orifice areas in smaller mounting diameters. Effective orifice areas are less predictable in the mitral position but adequate to provide substantial hemodynamic improvement in patients with mitral valve disease. The Ionescu valve shares the favorable characteristics (freedom from thrombo-embolism, relative resistance to infection) of the other bioprostheses available. Further use and study with comparison to other prostheses is recommended.

COMPARATIVE HEMODYNAMIC ASSESSMENT OF HANCOCK AND CARPENTIER-EDWARDS PORCINE XENOGRAFTS IN THE AORTIC POSITION

James A. Joye, MD; Todd M. Grehl, MD, FACC; Garrett Lee, MD; Anthony N. DeMaria, MD, FACC; Fred Harris, MD; Arthur J. Lurie, MD, FACC; Alan Gorang; Marilyn Hanna, RN; Edward J. Hurley, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis, California

Hancock porcine xenografts (H) have low hemolysis and thromboembolism risks compared to mechanical valves; their flexible stent and glutaraldehyde preservation have extended durability >5 years. However hydraulic function is reported compromised by suboptimal internal/external diameter. The thin-walled stent of the Carpentier-Edwards xenograft (CE) provides a potentially larger orifice. Thus this clinical study compares aortic CE to H by post-op catheterization. In 9 patients (pts) CE (annulus diameter 23-27 mm) had peak systolic gradient 20 mm Hg (range 3 to 40), mean gradient 18 mm Hg (8 to 32), aortic valve area 1.52 cm^2 and index 0.80 cm^2/M^2, left ventricular end-diastolic pressure (LVEDP) 9.4 mm Hg, and cardiac index (CI) 2.94 $L/min/M^2$. In 13 pts H (annulus diameter 21-27) had peak gradient 16 (0 to 24), aortic area 1.51 and index 0.99, LVEDP 10, CI 2.62. In addition, post-op CE and H angiographic ejection fractions, circumferential fiber shortening velocities, and left ventricular end-diastolic volumes were similar. CE compared to H variables by total group or annulus size: all $p > .05$. One CE and 1 H pt had mild aortic regurgitation. Thus, despite recent development of thin-walled stent in CE heterografts, no clinical or objective hemodynamic advantage over H was observed. The possibility remains that improved function may pertain to CE in the 19-21 mm size range.

CLINIC AND HEMODYNAMIC EVALUATION OF 118 PATIENTS UNDER GOING MITRAL FLEXIBLE RING ANNULOPLASTY.

José L. Pomar, M.D.; Alvaro Figueroa, M.D.; Alberto Ochoteco, M.D.; José L. Ubago, M.D. and Carlos G. Durán, M.D. Ph.D. Centro Médico Nacional Valdecilla. Universidad de Santander. Santander. Spain.

Reconstruction of all pathological mitral valves -unless heavily calcified- is always attempted at our Institution. An essential step in this conservative procedure is a selective annulus reduction using our totally Flexible Ring which does not interfere with the physiological annular movements. 501 mitral patients were operated between January 1975 and June 1977. In only 45% of them a replacement was required. 118 patients had a Flexible Ring inserted in the mitral position, 30 of them underwent tricuspid and 35 aortic associated surgery. In the group of 88 patients without tricuspid disease (27 with concomitant aortic surgery) no hospital and only one late death (carcinomatosis) occurred. In the group with simultaneous tricuspid annuloplasty there were 2 early and one late deaths. Follow-up is 3 to 33 months. 3 non fatal thromboembolic accidents have been detected. All 114 survivors moved to Class I or II except 4 patients. 40 cases have been recatheterized : the basal mean transmitral gradient dropped from 16.7 (± 7.8) to 9.9 (± 4.1) and after volume load from 21.9 (± 8.2) to 13.7 (± 5.9). Angiographically 10 patients had a significant regurgitation and 7 had to be reoperated without mortality, performing a valve replacement (3) or ring resuture (4). In conclusion, it is felt that this technique is a safe, stable and therefore valuable adjunct to the conservative surgery of the mitral valve.

PLASMA VASOPRESSIN LEVELS AND URINARY ELECTROLYTE CONTENT DURING CARDIOPULMONARY BYPASS.

Daniel M. Philbin, M.D., F.A.C.C.; and Cecil H. Coggins, M.D.; Massachusetts General Hospital, Boston, Mass.

We have previously reported high levels of plasma vasopressin (VP) during cardiopulmonary bypass (CPB) with light halothane anesthesia. This study was undertaken to determine the effect of deeper anesthesia on VP and urinary electrolytes in 14 pts. who were studied before, during and immediately after CPB. In Group I (halothane anesthesia) VP was elevated above control during surgery (82.4±23 pg/ml-$p<0.01$) and bypass (172.4±23 pg/ml-$p<0.001$) and gradually declined following CPB (89.3±16 pg/ml-$p<0.01$). Urine Na+ rose during CPB (127±4 meq/L -$p<0.01$) and urine K+ declined (30±8 meq/L-p <0.01). In Group II (morphine anesthesia 2mgm/kg) VP did not rise until CPB (58.3±16 pg/ml-$p<0.01$) again falling after CPB (21±5 pg/ml-$p<0.05$). During CPB urine Na+ increased (98±14 meq/L-$p<0.01$) and urine K+ declined (57±12 meq/L-N.S.). The rise in VP was greater in Group I than Group II ($p<0.01$)as was the rise in urine Na+ ($p<0.05$) and the fall in K+ ($p<0.01$) during CPB. These data suggest that the VP rise is a stress response which can be attenuated by deeper morphine anesthesia. It also suggests that the Na+ diuresis during CPB is VP related.

PULSATILE FLOW DYNAMICS DURING STRESS IN PATIENTS WITH AORTIC PORCINE HETEROGRAFTS AFTER 1 YEAR.

Wilmer W. Nichols, PhD, Leonard G. Christie, MD, Carl J. Pepine, MD, FACC, R. Charles Curry, MD, and C. Richard Conti, MD, FACC, U. of Florida, Gainesville, Fla.

Aortic root blood flow characteristics were examined during isoproterenol stress in 7 patients with ejection fractions (EF) >50% 12 months after aortic valve replacement with porcine heterografts and compared to 7 pts. with EF >50% and normal aortic valves. Pulsatile aortic root blood flow velocity waveforms were measured with an electromagnetic catheter-tip velocity transducer. Measurements of stroke volume (SV), peak blood flow velocity (PV) and acceleration (MA), ejection time (ET) and mean aortic pressure (AoP) were made under control resting conditions and during the intravenous injection of 3 µgm isoproterenol. Only two pts. had resting valvar gradients (6, 17 mm Hg.) while none had insufficiency by pulsatile waveform analysis or angiography.

RESULTS:	Normal	Porcine	p
HR(bpm)	99±5.3	94±7.0	NS
SV(cc)	92±7.3	95±10.8	NS
PV(cm/sec)	88±19	113±18	NS
MA(cm/sec^2)	2144±408	2832±313	NS
ET(msec)	234±11.2	225±9.8	NS
AoP(mmHg)	78±4.9	91±8.5	NS

CONCLUSIONS: During stress, as well as under resting conditions, aortic root velocity waveforms in pts. with porcine valves after 1 year were not significantly different from those with normal valves. However, pts. with porcine heterografts tended to have higher PV and MA than normals possibly related to the effects of unloading a hypertrophic ventricle. The normal flow dynamics of the aortic porcine heterograft may contribute to the low incidence of thromboemboli and to the longevity of the valve.

COMPARISON OF CARDIAC INDEX IN CHILDREN FOLLOWING NORMOTHERMIC AND HYPOTHERMIC REPAIR OF TETRALOGY OF FALLOT AND VENTRICULAR SEPTAL DEFECT

Peter Lang, MD; Carl W. Chipman, RN; Roberta G. Williams, MD; William I. Norwood, MD; Aldo R. Castaneda, MD
Children's Hospital Medical Center, Boston, Massachusetts

Cardiac index(CI)was measured by the thermodilution technique using a 2 Fr thermistor within 2 hours of intracardiac repair in 25 patients with tetralogy of Fallot(TOF) and 16 after transatrial closure of ventricular septal defect(VSD). Deep hypothermic circulatory arrest(DH)was employed in 18 patients(TOF 10, VSD 8); the remainder were repaired using normothermic cardiopulmonary bypass (NCPB). There were no early or late deaths. None had evidence of a residual intracardiac shunt or significant right ventricular outflow obstruction. Significant differences in CI were found between patients undergoing VSD (mean 3.58 ± 0.88)and TOF(mean 2.51 ± 0.75)repair with $p < 0.001$. Significant differences in CI were measured between the DH and NCPB patients in each category. In the VSD group mean CI was 4.14 ± 0.61 in NCPB and 3.03 ± 0.76 in DH patients($p<0.01$). In TOF values were 2.71 ± 0.85 and 2.21 ± 0.46 in NCPB and DH patients($p<0.1$). Significant differences in CI were also noted when comparing all NCPB patients(mean 3.21 ± 1.03)with all DH patients(mean 2.57 ± 0.73)with $p<0.025$. Although we have no explanation for the differences in CI between the NCPB and DH groups the decreased CI in TOF relative to VSD patients may reflect added disability caused by right ventriculotomy and right ventricular outflow patches.

THE ADULT FOLLOWING INTRACARDIAC REPAIR OF TETRALOGY OF FALLOT (TOF). Arthur Garson,Jr., M.D., Dan G. McNamara, M.D., FACC, Denton A. Cooley,M.D., FACC, Department of Pediatrics (Cardiology) Baylor College of Medicine, Texas Children's Hospital and Texas Heart Institute, Houston.

Each year in the USA, an estimated 2000 patients (pts) with surgically repaired TOF are reaching adulthood. This study provides follow-up data of relevance to physicians concerned with adult pts. We reviewed the current status of 233 pts born more than 15 yrs ago, who had had repair of TOF at median age 9.7 yrs(range 11 mo to 36 yrs). There were 27 surgical deaths (12%) and 11 late cardiac-related deaths (59%). Death was not related either to age at operation or prior anastomosis. Eight of the 11 late deaths occurred suddenly and in each,we had previously documented elevated right ventricular systolic pressure(RVSP)as well as PVCs. Of the 95 pts who responded to a questionnaire, 84 denied symptoms, 28 were married, and 44 were students. Of the 51 who were no longer students,34 had attended college and all who were not homemakers were employed.Cardiac catheterization(cath) revealed an unsatisfactory hemodynamic result in 39/120 pts, 28 of whom were asymptomatic. The poor result was due to a left-to-right shunt of $\geq$1.5:1 through a persistent VSD in 8 pts, persistent RV outflow obstruction with RVSP $\geq$ 60 mm Hg in 25 pts, and pulmonary vascular obstructive disease in 6 pts. Of the 21 pts with PVCs, 17 underwent cath: 15 had RVSP $\geq$ 60 mmHg and 2 had elevated RV end-diastolic pressure.Pulmonary regurgitation was not related to PVCs. We conclude: 1. Clinical assessment alone is nonpredictive of the hemodynamic result and thus cath is indicated in all pts. 2. Persistent elevation of RVSP $\geq$ 60 mm Hg, especially if associated with PVCs, places the pt at risk for sudden death. All PVCs should be treated and the RV outflow obstruction relieved if possible. 3. Over 80% of adults with TOF can lead a normal life without impairment in intellect, exercise tolerance, or fertility.

ATYPICAL AORTIC VALVE STENOSIS - PART OF DIFFUSE CARDIOVASCULAR DISEASE - RECOGNITION AND SURGICAL TREATMENT

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National Heart Hospital, Westmoreland Street, London, England

14 patients aged 3-16 years with congenital aortic valve stenosis were different from the majority of young patients needing valvotomy. This special group need recognition as conventional valvotomy is probably not the ideal treatment owing to the problems of the inevitable later operation. These patients usually present earlier than the others, have thick cartilaginous tricuspid valves with a small aortic root, slight supravalvar narrowing and marked subvalvar hypertrophy with disproportionate septal thickening. Biopsy of the ascending aorta shows severe "higgledy-piggledy" disorder of the musculo-elastic media whereas the aorta was normal in 5 with the commoner pliable domed aortic valve stenosis. Aortic valvotomy may initially relieve symptoms. However, at re-operation there is difficulty in relieving the diffuse left ventricular outflow obstruction which forms. As a primary procedure in this group we have replaced the whole aortic root and valve with an adult sized homograft and re-implanted the coronary arteries in 10 children with one death. The rest are well with no resting gradients across the outflow and patent coronary arteries 1-3 years later. Such a procedure may make left ventricular aortic bypass obsolete.

See Addendum

THURSDAY, MARCH 9, 1978
AM
CORONARY ARTERY DISEASE
8:30 to 12:00

INTRAOPERATIVE IDENTIFICATION OF SPECIALIZED CONDUCTION TISSUE IN PERSISTENT COMMON ATRIOVENTRICULAR CANAL AND STRADDLING ATRIOVENTRICULAR VALVES

Barry R. Keeton, MRCP; James D. Maloney, MD, FACC; J. T. Lie, MD, FACC; Gordon K. Danielson, MD, FACC; Dwight C. McGoon, MD, FACC; Robert B. Wallace, MD; Robert H. Feldt, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, MN.

The anatomy of the conduction tissue (CT) in the usual atrioventricular (AV) canal defect is well known. In hearts with coexistent anomalies of atrial situs, AV connection, or straddling AV valve, the position of CT is less clearly defined. We present our experience with the intraoperative electrophysiologic delineation of the CT in 13 patients (pts) with such defects and assess the value of the preoperative electrocardiogram in predicting its position. Of the 7 pts with concordant AV connections, 6 had posterior CT, irrespective of atrial situs, straddling right AV valve in 1 pt, straddling left AV valve in 1 pt, and dextrocardia in 1 pt. The remaining pt had AV concordance but crisscross AV relations, and the CT was not identified posteriorly. Of the 3 pts with discordant AV connections, 2 had posterior CT. One of the 2 had a complete AV canal (type C), and the other had a straddling right AV valve and crisscross AV relations. The 3rd pt had a straddling left AV valve and anterior CT. Of the 3 pts with situs ambiguus and common AV valve, 2 were successfully mapped. One had CT both anteriorly and posteriorly. This is the first occasion in which we have achieved electrophysiologic identification of this previously histologically described entity. The other pt had posterior CT. Pathologic study of 2 of these pts has been performed. The association of AV canal defect with abnormalities of AV connection, ventricular relations, and atrial situs leads to difficulty in predicting the site of the CT. Electrophysiologic identification during surgery has been of value.

SMOKING AND HIGH DENSITY LIPOPROTEINS AND CORONARY CHANGE IN TWO AND THREE VESSEL DISEASE

Miguel E. Sanmarco, MD; Ronald H. Selvester, MD; Samuel H. Brooks, ScD; David H. Blankenhorn, MD, FACC, USC-Rancho Los Amigos Campus, Downey, Calif.

The influence of risk factors on progression of obstructive coronary disease (POD) was assessed by serial coronary arteriography in 35 men (pts) age 41 to 52 with two and three vessel coronary disease restudied at 14 $\pm$ 3 months. Weight, blood pressure, plasma lipids, lipoprotein fractionation, and smoking habits (SM) were obtained every three months during a clinical trial of diet and exercise. POD, defined as any increase in obstruction greater than 35% or progression to total occlusion occurred in ten pts (eight cigarette smokers) while 25 pts exhibited insignificant or no change (six cigarette smokers). The degree of coronary change was correlated to the risk factors by multivariate stepwise regression analysis. Cholesterol (Chol), triglyceride (TG), and blood pressure were not related to coronary change. (Averages of these values were within normal limits). Significant correlates of coronary change were smoking ($p < 0.001$), age ($p < 0.05$), and αlipoprotein ($p < 0.05$). The correlation with age and αlipoprotein (α) was negative, that is younger pts with low α progressed faster. Also noted was a significant negative correlation between α and SM, Chol, TG, and physical activity (each with a $p < 0.05$).

Premature onset of clinical coronary disease appears to carry an ominous prognosis which may be improved by cessation of cigarette smoking and possibly by exercise and diet modification. The apparent protective effect of elevated α lipoproteins may be mediated through enhancement of the lipid transport system due to changes in the ratio of high to low density lipoproteins.

LEFT VENTRICULAR PRESSURE-VOLUME CHANGES DURING SPONTANEOUS ANGINA PECTORIS

B.Sharma, M.D.; M. Hodges, M.D.,FACC; R.Asinger,M.D.; R. Johnson,M.D.; J.F.Goodwin,M.D.,FACC, Hennepin County Medical Center and the University of Minnesota, Minneapolis, MN and Hammersmith Hospital, London, England.

Most studies evaluating LV pressure and volume during angina have utilized atrial pacing to produce ischemia. Although these studies have been criticized because they may not reflect the changes in volume that might occur during spontaneous angina pectoris (SAP), no study on LV volume during SAP has so far been reported. We measured LV pressure, volume and wall motion in 14 patients when they developed SAP during cardiac catheterization. In every patient control measurements had previously been made; further measurements were made after nitroglycerin (NTG) had relieved pain. Subsequently coronary angiography showed significant 2 or 3 vessel disease in all 14 patients. The ST-segment was depressed in every patient during angina (ave. = -0.26±.13 mv; mean±SD); wall motion study revealed either a new area or further extension of an already existing area of asynergy in all patients.

STATE	LVEDP (mmHg)	EDV (ml/m^2)	ESV (ml/m^2)	EF (%)
REST	18±8	80±20	36±14	56±12
	p<.001	p<.01	p<.001	p<.001
SAP	34±9	91±28	53±25	44±15
	p<.001	p<.03	p<.02	p<.01
NTG	13±5	83±24	30±14	64±14

This study reveals that EDV significantly increases with the rise in LVEDP during SAP (associated with significant ST depression and abnormal wall motion), indicating severe LV dysfunction. Nitroglycerin promptly reversed the depressed cardiac function induced by SAP. These pressure-volume changes are different from those of angina induced by atrial pacing as reported in previous studies.

CORRELATIONS BETWEEN LATE VENTRICULAR DYSRHYTHMIAS AND INFARCT SIZE

Ali A. Ehsani, MD; Mary K. Campbell, RN; Edward M. Geltman, MD; Robert Roberts, MD, FACC; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri

Enzymatically estimated infarct size index (ISI) appears to be a determinant of ventricular dysrhythmia and depressed left ventricular ejection fraction within the first ten hours, and of mortality within one month after acute myocardial infarction. To determine whether ISI is also related to later events, we followed 63 patients with enzymatically estimated infarct size, ≤60 years of age who had sustained an initial infarction uncomplicated by an extension during the initial admission and who survived for at least five days. ISI in survivors was 22 ± 2 (mean ± SE) CK-g-eq/m^2 BSA compared to 71 ± 7 in the five patients who succumbed ($p < .001$). There was no correlation between ISI and ejection fraction assessed more than four months after infarction with ^{99m}Tc-albumin in 36 patients. The frequency of premature ventricular complexes (PVCs) in 28 patients (none of whom had sustained additional infarctions) assessed by automated analysis of 24-hour Holter tapes obtained between 2 and 12 months after infarction averaged 241 ± 117/24 hours in patients with small infarcts (ISI < 15) compared to 1292 ± 840 in patients with large infarcts (ISI ≥ 15) ($p < .05$). These results indicate that among relatively young patients with initial infarction, enzymatically estimated infarct size presages not only ventricular electrical instability and function during the acute episode but also the severity of ventricular dysrhythmia as long as one year after myocardial infarction.

NONINVASIVE DIAGNOSIS OF ISCHEMIC CARDIOMYOPATHY BY FLUOROSCOPIC DETECTION OF CORONARY ARTERIAL CALCIFICATION

Allen Johnson, MD FACC; Stuart Laiken, MD; Ralph Shabetai, MD FACC, Univ of Calif and VA Hosp. San Diego, Calif.

Severe coronary artery disease (CAD) may give rise to progressive cardiomegaly and congestive heart failure (CHF) in the absence of a history of myocardial infarction. Coronary arteriography may be necessary to distinquish the resulting ischemic cardiomyopathy from nonischemic cardiomyopathy. To assess the value of fluoroscopic detection of coronary arterial calcification (CorCa^{++}) in this differential diagnosis, all patients seen over a 3 year period with severe CHF and cardiomegaly who underwent catheterization had cardiac fluoroscopy prior to coronary arteriography. Those with a history of myocardial infarction or significant valvular disease were excluded. The 24 remaining patients all had evidence of marked hemodynamic compromise (LVEDI>110ml/M^2, EF<.35). 10 of these patients had CorCa^{++} at fluoroscopy. All 10 had abnormal coronary arteriograms: 6 had 3 vessel disease, 3 had 2 vessel disease, and each had left anterior descending involvement. Each of the 14 patients without CorCa^{++} had normal arteriograms. The group with CAD had a mean age of 52 (range 39-68), 50% had typical or atypical chest pain, 80% had at least one coronary risk factor, and 30% had ECG Q waves. The corresponding values for the nonischemic group were: age 44 (range 26-62), 21% with chest pain, 57% with at least 1 risk factor, and 43% with Q waves. Although chest pain and risk factors were more common in those with CAD, no clear separation could be made clinically between the 2 groups of pts. We conclude that fluoroscopic detection of CorCa^{++} provides a reliable noninvasive method for distinguishing patients with ischemic cardiomyopathy from those with nonischemic cardiomyopathy, particularly when the diagnosis is not clinically apparent.

ASYMPTOMATIC HEALTHY PERSONS WITH FREQUENT COMPLEX VENTRICULAR ECTOPY AND CORONARY ARTERY DISEASE.

Harold L. Kennedy, MD, MPH, FACC; Janet E. Pescarmona; Richard J. Bouchard, MD; and Dennis G. Caralis, MD, Department of Cardiovascular Services and Clinical Investigations, U.S. Public Health Service Hospital, Baltimore, Maryland.

To determine if frequent complex ventricular ectopy detected by 24 hour ambulatory electrocardiography was an indicator of asymptomatic coronary artery disease (CAD) in apparently healthy subjects, forty-seven asymptomatic patients incidentally discovered to have frequent complex ventricular ectopy were clinically evaluated and found to be otherwise normal. Twenty subjects (17 men, 3 women, mean age 49 ±12 yrs) granted informed consent to study by cardiac catheterization and coronary arteriography. Results disclosed patients with significant CAD (≥50% luminal narrowing); subclinical CAD (≤50% luminal narrowing) and normal coronary arteries. Mean left ventricular end diastolic volumes (LVEDV) and systolic volumes (LVESV), ejection fractions (EF), and mean left ventricular end diastolic pressures (LVEDP) were examined. Holter monitoring (24 Hr) measured mean frequency and types of ventricular ectopic beats (VEB).

Results showed:

	Significant CAD	Subclinical CAD	Normals	P Value
No. of Patients(%)	6(30)	3(15)	11(55)	n.s.
LVEDV(cc/M2)	88 ±8	66 ±7	80 ±5	n.s.
LVESV (cc/M2)	34 ±3	24 ±3	31 ±4	n.s.
EF(%)	63 ±2	63 ±2	61 ±3	n.s.
LVEDP(mm Hg)	12 ±9	14 ±2	14 ±2	n.s.
VEB(Beats/Hr)	442 ±96	642 ±388	349 ±56	n.s.
Multiform VEB(%)	5(86)	3(100)	7(64)	n.s.
VEB Couplets(%)	4(67)	3(100)	8(73)	n.s.
VEB Tachycardia(%)	2(33)	0(0)	2(18)	n.s.

In this study of asymptomatic apparently healthy persons with frequent complex ventricular ectopy:

a) the majority of patients did not have significant CAD (70 Percent)
b) mean frequency or complex types of ventricular ectopy could not predict the presence or absence of CAD
c) left ventricular function measurements could not predict the presence or severity of CAD or frequent complex ventricular arrhythmia.

CLINICAL AND ANGIOGRAPHIC FEATURES OF CORONARY ARTERY DISEASE IN YOUNG WOMEN

David D. Waters, MD, FACC; Christine Halphen, MD; Pierre Théroux, MD, FACC; P. Robert David, MD; Henry F. Mizgala, MD, FACC, Montreal Heart Institute, Montreal, Quebec

To determine if the characteristics of coronary artery disease (CAD) in young women differ from those in other patient populations, we studied 239 women <45 years old undergoing left ventricular and coronary angiography for suspected CAD. 112 had normal coronary arteries (NCAs), 56 had one vessel, 22 two vessel, 26 three vessel disease and 23 stenoses <50% of the luminal diameter. Of those with stenoses ≥50%, 79% had LAD, 36% circumflex, 51% right and 8% left main coronary artery involvement. A segmental wall motion abnormality (WMA) was found at ventriculography in 41, 64 and 69% of those with one, two and three vessel disease respectively. 3 of the 112 with NCAs and 2 of the 23 with stenoses <50% had WMAs; 4 of these 5 had had clinically documented infarctions. The WMA was anterior in 19 of 21 women taking oral contraceptives but in only 20 of 35 not taking these drugs.* Factors more common in women with significant CAD, compared to those with NCAs, were hyperlipidemia (77 vs 33%*), diabetes (19 vs 2%*), hypertension (41 vs 11%*), smoking (87 vs 59%*), oral contraceptives (37 vs 27%) and a high familial incidence of CAD (77 vs 63%*). Only 7% (4 of 57 women) with <2, but 55% of those with >2 of these risk factors had CAD.* The last 140 women studied had treadmill exercise tests one day prior to angiography. The false positive rate was 26% and the false negative rate was 47%.

We conclude that in this population CAD is very rare in the absence of risk factors. Exercise testing does not accurately predict the presence of CAD. At angiography one vessel disease, particularly of LAD, predominates. MI with NCAs is uncommon. When WMAs occur with oral contraceptives the site is inexplicably anterior in 90%. (*$p<0.05$)

RELATIVE EFFECTS OF ASPIRIN ON PROSTAGLANDIN MODULATION OF CORONARY BLOOD FLOW AND PLATELET AGGREGATION

Lewis C. Lipson, MD; Robert O. Bonow, MD; Norine L. Capurro, PhD; Robert E. Goldstein, MD; N. Raphael Shulman, MD; Stephen E. Epstein, MD, FACC, NHLBI, NIAMDD, Bethesda, Md.

Arachidonic acid (AA) is the common fatty acid precursor of prostaglandins (PG), some of which cause platelet aggregation (PA) and vasoconstriction, others vasodilatation and inhibition of PA. It has been proposed that PA might be the initiating event in formation of the atherosclerotic plaque. Thus, aspirin (ASA), as an inhibitor of PA, is currently being tried in prevention of ischemic heart disease. However, ASA blocks the first step of PG synthesis; it might thereby inhibit PG-mediated coronary vasodilatation and offset beneficial actions of inhibition of PA. The relative sensitivity of PA and PG-mediated coronary vasodilatation to ASA inhibition remains uncertain. We therefore investigated the effects of increasing doses of ASA on ADP-induced PA and AA-induced increments in coronary blood flow (CBF). In 7 open-chest dogs, intracoronary AA, .1-3mg, produced dose related increments in CBF that were progressively inhibited by iv ASA, .3-3 mg/kg. A 1 mg dose of AA was 24, 80, and 89% inhibited by ASA doses of .3, 1, and 3 mg/kg respectively. Likewise, while ASA 3 mg/kg completely inhibited PA induced by even high ADP concentration (2.3×10^{-4}M), ASA .3mg/kg only inconsistently inhibited PA induced by low (threshold) concentrations of ADP (5.1×10^{-6}M). Thus inhibition of PA and of AA-induced increase in CBF showed similar sensitivity to ASA with respect to threshold dose and maximum effect. We conclude 1) that ASA produces a dose-dependent inhibition of PG-mediated coronary vasodilatation and 2) that there appears to be no dose of ASA that selectively blocks PA without concomitantly blocking PG-mediated increments in CBF.

STUDIES ON THE ROLE OF CHRONIC PROPRANOLOL THERAPY IN ALTERING PLATELET AGGREGATION IN CORONARY DISEASE PATIENTS BEFORE, DURING AND AFTER ACUTE ISCHEMIA.

Jawahar Mehta, MD, Paulette Smedresman, MD, and Carl J. Pepine, MD, FACC, University of Florida College of Medicine and VA Hospital, Gainesville, Florida.

Propranolol has been shown to decrease platelet aggregation (PAg) in coronary heart disease (CHD) patients. To evaluate the role of chronic propranolol therapy on PAg in CHD patients during acute ischemia, blood was collected from the aorta (Ao) and coronary sinus (CS) during cardiac catheterization studies in eight patients. Four patients were not taking propranolol (group A) while four were on chronic propranolol therapy (group B). Blood samples were obtained before, during and following tachycardia induced ischemia associated with ST segment changes and symptoms. PAg was assessed by Bio-data Aggregation Profiler using ADP stimulation.

PAg was 70% and 75% lower in the Ao and CS respectively, in group B, compared to group A (both $p<.05$). In group A, during ischemia, PAg was unaltered in Ao but increased 200% ($p<.01$) in the CS and returned to control following relief of ischemia. In group B, PAg remained unchanged in the Ao during ischemia but increased only 41% ($p<.05$) in the CS with ADP and returned to control following relief.

While chronic propranolol therapy lowers PAg in both the Ao and CS of CHD patients, PAg in the CS blood increases significantly during acute ischemia. This ischemia related increase in CS PAg is transient and rapidly reverses following relief of ischemia. However, the PAg increase in patients on propranolol therapy does not reach the same magnitude as observed in patients not taking propranolol. These data indicate that propranolol-related changes in PAg may play a role in clinically beneficial response in CHD patients.

PLATELET AGGREGATION IN STENOSED CORONARY ARTERIES: MECHANISM OF SUDDEN DEATH? John D. Folts, Ph. D., George G. Rowe, M. D., FACC, Dept. of Med., Univ. Wisc. Med. School, Madison, WI 53706.

Many sudden coronary deaths do not have an acute fibrin thrombus at autopsy. In 64 open chest dogs with 60-80% stenosis of a left coronary artery branch, cyclical reductions in coronary blood flow (CRBF) occurred, followed by an abrupt return to control levels. These CRBF occurred 8 ± 5 times/hr with an average flow reduction of 72 ± 21%, and are believed due to platelet (Pt) aggregated "plugs" forming in the stenosed coronary artery periodically, narrowing the lumen, and causing increased obstruction. The platelet plug then breaks loose, restoring the flow. We feel these CRBF are not caused by vascular muscle spasm. CRBF are abolished with I. V. aspirin 30 mg/kg, or propranolol 4 mg/kg, or indomethacin 15 mg/kg, but not with heparin 6,000 U or the antispasmodic vasodilators, persantine 0.8 mg/kg, papaverine 1.0 mg/kg or nitroglycerin .06 mg/kg. CRBF are exacerbated by I. V. adrenalin 50μ gm which would lower Pt cyclic AMP levels and promote Pt aggregation. The adrenalin exacerbated CRBF are abolished with 35 mg/kg of aminophylline which would raise Pt cyclic AMP levels. Most of the known coronary risk factors cause an increase in human platelet aggregation, therefore platelet aggregates may form in stenosed human coronary arteries and acutely reduce coronary blood flow and precipitate a fatal arrhythmia.

INTERVENTION VENTRICULOGRAPHY: COMPARISON OF POST EXTRASYSTOLIC POTENTIATION AND NITROGLYCERIN IN THE PRESENCE OF ACUTE CORONARY STENOSIS

Gerald L. Wolf, PhD, MD, David D. Shaw, PhD, Harold A. Baltaxe, MD, FACC, and Robert S. Eliot, MD, FACC, University of Nebraska Medical Center, Omaha, Nebraska

Post extrasystolic potentiation (PESP) and administration of nitroglycerin (TNG) have been shown capable of revealing reversible dyskinesia during ventriculography (VG). The superiority of one or the other technique has not been demonstrated. We, therefore, performed PESP and PESP + TNG ventriculograms on anesthetized animals in which severe proximal stenosis of the anterior descending or circumflex coronary artery was produced. The stimulus for the premature beat was introduced, at the peak on the T wave, through a RV pacing catheter. All stimuli were introduced on the sixth beat after the VG injection was begun. Ventricular volumes (EDV,ESV), ejection fraction (EF) and segmental wall motion for the potentiated beat were compared to at least two sinus beats prior to the potentiated beat by computer methods. Coronary stenosis resulted in increases in EDV, ESV and EDP and decreases in EF and segmental wall motion of myocardium supplied by the stenosed artery. The PESP beat showed a significantly increased EF and greater motion in the dyskinetic wall indicating an ischemic but still viable muscle mass. After TNG infusion sinus beats during the VG showed a characteristic fall in EDV and EDP and an increase in EF and motion of the dyskinetic wall. However the PESP beat showed a further increase in EF and wall motion. These results indicate that, at least in this model of acute ischemia, PESP is a superior stimulus in eliciting an augmented contractile response from ischemic myocardium.

SMALL STIFF HEART IN DIABETES MELLITUS.

Samuel Zoneraich, M.D., F.A.C.C., Gertrude Silverman, M.D. and Olga Zoneraich, M.D., F.A.C.C., State University of New York at Stony Brook, Clinical Campus at Queens Hospital Center-Long Island Jewish Medical Center.

The small stiff heart (ssh) causing sudden onset of acute pulmonary edema (a.p.e.) is found in diabetic patients (d.p.).

Paraffin blocks of 82 hearts were obtained from 50 diabetic nonhypertensive patients (dp) and from 32 non diabetics (nd). Four blocks were taken from 7 areas. Each block was sectioned at 6 μ and 7 sections were stained with hematoxylin-eosin and Verhoeff-Van Giessen. The heart was enlarged (over 400 gms) in 32 d.p. with small coronary arterial (Sca) involvement (64%), 20 of whom had occlusion of extramural coronaries (ec). Four d.p. (8%) with severe triple occlusion of ec and Sca disease had Ssh (350 gms or less). Sca (20-150 μ) involvement consisted of a) endothelial proliferation (mounds, cushions, humps), papillary projections and bridges b) subendothelial fibrosis with elastica proliferation c) exudative deposits of hyalin in the intima and significant lesions of intramural arterioles bordering the A-S and A-V nodes and d) atheromatous thickening with cholesterol clefts and hyalinized intima. The myocardium (m) showed extensive fibrosis (f) and scarring (s). Ten d.p. (20%) with Sca disease only, had hearts of normal weight. The m. was free of diffuse f. and s. Six pts had mild heart failure. In conclusion Ssh with severe heart failure disease is seen when both severe ec and Sca causing a.p.e. are present in patients with diabetes mellitus.

DURATION OF ACTION OF PROPRANOLOL IN ANGINA PECTORIS.

U. Thadani, MB, FRCP(C), J.O. Parker, MD, FACC, Queen's University, Kingston, Ontario, Canada.

The duration of action of single oral doses of 80 and 160 mg propranolol (P) on heart rate (HR), systolic blood pressure (SBP), and exercise tolerance were studied in 11 patients with stable angina pectoris (AP). After control (O), multistage treadmill exercise test (TET), P80 mg was given orally and TET repeated after 1, 2,4,8,12, and 24 hours (h). Seventy-two h later, this study was repeated after P 160 mg. The end-point pre-P was moderate AP and post-P was moderate AP or fatigue. Blood for plasma P was collected before each TET. The mean results are shown in the table:

P 80 mg	0h	1h	2h	4h	8h	12h	24h
PC	0	28	37	37	18	6	0
HR	131	114**	112**	113**	118**	122*	128
SBP	171	136**	134**	136**	146**	154**	166
WT	432	505**	548**	518**	505**	465	454
P 160 mg							
PC	0	59	101	90	49	23	3
HR	130	104**	103**	108**	113**	118**	126
SBP	168	133**	127**	127**	136**	146**	163
WT	438	559**	572**	559**	535**	495*	478

HR in beats/min, PC = plasma concentration in ng/ml, SBP in mmHg, WT = walking time in sec, * = P<0.05, ** = P<0.01 compared to 0 h.
Plasma half life for P 80 was 4.0 h and for P 160 was 4.3 h, but the biological effects of P 80 and P 160 persisted for 8 and 12 h respectively. This suggests that twice daily dosage of P 80 and P 160 mg should be effective in the treatment of angina pectoris.

THURSDAY, MARCH 9, 1978
AM
ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY—III
8:30 to 12:00

PROTECTIVE EFFECT OF VERAPAMIL ON VENTRICULAR VULNERABILITY DURING CORONARY ARTERY OCCLUSION AND REPERFUSION.

Wesley W. Brooks, MS; Richard L. Verrier, PhD, FACC; Bernard Lown, MD, FACC, Cardiovascular Research Laboratory, Department of Nutrition, Harvard School of Public Health, Boston, Mass.

Vulnerability to ventricular fibrillation (VF) during coronary artery occlusion (CO) and reperfusion (R) is thought to be mediated by differing mechanisms. Whereas enhanced sympathetic tone is thought to be largely responsible for VF during CO, vulnerability during R has been attributed to washout products of cellular ischemia. The effect of verapamil, a slow channel blocking agent, on the VF threshold during CO and R was studied in 20 dogs using a single 10 msec stimulus. Balloon catheters were placed around the left anterior descending coronary artery 3 days prior to testing. Under chloralose anesthesia the VF threshold was determined in 7 dogs before CO, throughout a 10-minute CO, and immediately on R. In a group of 7 dogs the VF threshold was tested, first with verapamil infusion (.01 mg/kg/min, i.v.) and during CO and R. Values are means ± SE. * = p <0.05 compared to control.

	VF threshold (milliamperes)			
	Pre-occlusion	Occlusion 2 min	Occlusion 8 min	Reperfusion 0-30 sec
Control	16 ± 2	6 ± 1	10 ± 2	4 ±1
Verapamil	15 ± 2	10 ± 1*	11 ± 1	9 ± 1*

In 6 additional normal dogs, verapamil significantly reduced the decrease in the VF threshold associated with stellate ganglion stimulation. We conclude that verapamil protects during both early CO and R and that this effect may be due to antagonism of sympathetic tone to the heart and to blockade of slow calcium channels.

EPICARDIAL MAPPING OF VENTRICULAR REENTRANT PATHWAYS IN THE LATE MYOCARDIAL INFARCTION PERIOD

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Epicardial activation sequence was mapped during ventricular arrhythmias (VA) induced by premature stimulation in 4 dogs 3-5 days after anterior descending coronary artery ligation. A 17 cm^2 rectangular grid of 48 equally spaced bipolar electrodes with 2 mm interpolar distance was applied to the infarct zone (IZ) and surrounding normal zone. Electrograms were recorded simultaneously with a multiplexing system and were computer processed. Activation times permitted detailed description of activation sequence in the IZ during the VA. Following the premature stimulation, activation fronts circumvented a central area of functional unidirectional block which was about 1 cm^2 in size. The reentrant paths were completed when delayed activation entered the central area and progressed through the previous site of block to reexcite the ventricle. The epicardial sequence and length of the reentrant pathway, as well as the QRS configuration of the reentrant beat, varied in the same animal. The conduction velocity, as suggested by the activation times, varied in different segments of the reentrant pathway. In some reentrant beats, activation times bridged the entire diastolic interval reflecting a predominant epicardial location of the reentrant path. During other beats, gaps in the epicardial activation times suggested intramyocardial segments of the reentrant pathway. The study has demonstrated a reentrant mechanism of VA at 3-5 days after coronary ligation and has clearly shown the feasibility of tracing reentrant paths by activation sequence mapping.

CRITICAL ROLE OF SUBENDOCARDIAL ACTIVATION IN THE GENESIS OF MALIGNANT VENTRICULAR TACHYCARDIA AND FIBRILLATION.

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Continuous electrical activity during diastole prior to ventricular premature complexes (VPC) or ventricular tachycardia (VT) is a critical determinant of ventricular reentry in acute myocardial infarction. However, the precise re-excitation pathway from the infarcted zone (IZ) to the normal tissue (NT) has not been shown. VPC, VT and ventricular fibrillation (VF) were produced in 11 open chest dogs by a ligation and perfusion techniques of the left anterior descending coronary artery. Lead II and 7 close bipolar and composite electrograms were simultaneously recorded from endocardial and epicardial surfaces in the IZ (Endo IZ and Epi IZ) and NT. Low frequency spikes as well as various Epi IZ conduction ratios (2:1, 3:1 and Wenckebach periods) inducing VPC and VT were observed. The highest degree of fragmentation was observed well within the Epi IZ with peripheral decrement. Ventricular pacing at single or multiple (simultaneous) points and rapid atrial pacing increased fragmentation. Endo IZ spikes, following the diastolic Epi IZ activity, were always observed prior to each ectopic activation of the adjacent NT. VF could be predicted by prior fragmentation of the Endo IZ electrograms. Continuous fibrillatory activity in the Epi IZ was transmitted to the NT only through prior activation of Endo IZ. It is concluded that (1) delayed activation in Epi IZ did not necessarily result in VPC or VT, (2) Endo IZ activity predictably preceded VPC, VT and VF, (3) VF occurred with prior fragmentation of Endo IZ electrograms, (4) Endo IZ appears to be the necessary link of reentry between the tissue of origin of reentrant activity (the Epi IZ) and the NT.

ENDOCARDIAL MAPPING OF VENTRICULAR TACHYCARDIA IN MAN

Mark E. Josephson, MD, FACC; Leonard N. Horowitz, MD; Ardeshir Farshidi, MD; Joseph F. Spear, PhD, FACC, John A. Kastor, MD, FACC; E. Neil Moore, DVM, FACC, University of Pennsylvania, Philadelphia, Pa.

Endocardial ventricular mapping (EVM) of 25 ventricular tachycardias (VT) was performed using electrode catheters (1 cm interelectrode distance). Mapping sites included the atrioventricular junction, coronary sinus, apex, midseptum, anterior wall, lateral inflow tract and outflow tract of the right ventricle (RV); and high, mid, and low septum, apex, lateral wall and posterior basal area of the left ventricle (LV); and at least one site within a LV aneurysm when present. Twelve VT had a left bundle branch block pattern (VT-LBBB) and 13 VT had a right bundle branch block pattern (VT-RBBB). In all VT-RBBB the earliest site of activation was in the LV or septum. In VT-LBBB the earliest site was either in the RV (4/12), the LV (6/12), or the septum (2/12). In all VT with QRS $\leq$140 msec (4/25) the site of origin was in the septum. In patients (pts) with LV aneurysms the site of origin of VT was always in the area of the aneurysm. All VT-LBBB arising from the LV originated in an aneurysm involving the septum. Spontaneous or pacing-induced QRS changes during VT were associated with alterations in the pattern of ventricular activation and in 3 pts continuing activity in an aneuyrsm was unaffected during the change in morphology. In 2 pts VT-RBBB changed to VT-LBBB upon the development of exit block. In 3 pts the site of origin predicted by EVM was confirmed intra-operatively by epi- and/or endocardial mapping. We conclude that EVM demonstrates the limitations of the surface ECG in localizing the site of origin of VT and may provide important data upon which the surgical treatment of VT is based.

DIVERSE ELECTROPHYSIOLOGICAL MECHANISMS UNDERLYING MALIGNANT VENTRICULAR DYSRHYTHMIA

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Both coronary occlusion and reperfusion result in malignant ventricular dysrhythmia in experimental animals and either may precipitate sudden death in man. In the present study, electrophysiological properties of the two dysrhythmias were delineated in 57 chloralose-anesthetized cats with proximal LAD occlusion and subsequent reperfusion 35 minutes later. Both coronary occlusion and reperfusion gave rise to reproducible bouts of malignant ventricular dysrhythmia. Simultaneous bipolar electrograms (epi-, myo-, and endocardial) from ischemic and normal zones were continuously analyzed by computer. Dysrhythmia after occlusion was preceded by slowed conduction in the ischemic electrode-zone (dV/dt decreased by 66$\pm$6% (mean$\pm$SE)), delayed endo- to epicardial conduction (290$\pm$91% of control), asynchronous depolarization (pulse width increased by 595$\pm$76%) a slow idioventricular escape rate elicited with maximal vagal stimulation (62$\pm$6 beats/min), exacerbation with rapid atrial stimulation, and shortening of the refractory period in ischemic zones (by 15$\pm$2%). In contrast, dysrhythmia after reperfusion was characterized by normalized conduction in the ischemic electrode-zone, normal endo- to epicardial conduction time (129$\pm$15% of control), a return to synchronous depolarization (pulse width = 126$\pm$13% of control), a rapid idioventricular escape rate (188$\pm$12 beats/min), suppression by atrial pacing, and no change in ischemic zone refractory period. Thus, dysrhythmia due to coronary occlusion alone appeared to depend on reentry in contrast to dysrhythmia following reperfusion in which enhanced ventricular automaticity was the apparent progenitor.

CONTINUOUS LOCAL ELECTRICAL ACTIVITY: Mechanism of Ventricular Tachycardia in Man

Mark E. Josephson, MD, FACC; Leonard N. Horowitz, MD; Ardeshir Farshidi, MD, University of Pennsylvania, Philadelphia, Pa.

Although the mechanism of most episodes or recurrent ventricular tachycardia (VT) is believed to be reentry, definitive proof of this hypothesis has heretofore been unavailable in man. Such proof would require the demonstration of a temporal relationship of the initiation and perpetuation of VT to the development of continuous electrical activity preceding the first and subsequent complexes of the arrhythmia. Using programmed ventricular stimulation and ventricular endocardial mapping we studied 3 patients in whom the initiation of VT was dependent upon the development of a critical degree of fractionation and delay in local left ventricular electrograms. When electrical activity spanned diastole VT ensued. Perpetuation of VT was associated with continuous electrical activity resembling "local fibrillation" while termination of VT required cessation of this continuous activity. That the continuous activity represented reentrant activity is supported by: a) the ability to initiate and terminate such activity, b) recording discrete diastolic and systolic activity by moving the catheter, and c) spontaneous termination. During sinus rhythm the electrogram recorded from the areas which subsequently developed continuous activity showed markedly fractionated and prolonged electrical activity exceeding 100 msec in duration, suggesting a substrate of asynchronous conduction through potential reentrant pathways. These observations of the temporal relationship of continuous activity with the development of VT strongly suggest the reentrant nature of this arrhythmia in man.

PERSISTENT ST-SEGMENT ELEVATION FOLLOWING ANTERIOR MYOCARDIAL INFARCTION: ASSESSMENT OF THE ROLE OF ISCHEMIA BY BODY-SURFACE POTENTIAL MAPS. (BSPM). B. Milan Horacek, PhD; Henry Gewirtz, MD; Eldon R. Smith, MD; Hermann K. Wolf, PhD; and Pentti M. Rautaharju, MD, PhD, FACC. Dalhousie University, Halifax, Nova Scotia, Canada.

Many patients (pts) have persistent ST-segment elevation (STE) following anterior myocardial infarction (AMI) - an abnormality which has been shown to reliably predict advanced LV asynergy. The genesis of the STE is unknown although observations that asynergy may be partially reversible, and that increased STE may occur with exercise, suggest that on-going ischemia may be operative. To assess this in more detail, BSPM (generated from simultaneous recordings from 117 torso sites) were obtained from 11 pts with AMI and persistent STE (all male; mean age 58 yrs) and 11 normals (N). BSPM were recorded before and at peak effect of 3 random interventions (Int), each designed to alter the myocardial oxygen (O_2) supply-demand ratio (40% O_2 for 20 min, 0.3-0.6 mg nitroglycerin sublingually, and 25% maximum handgrip for 5 min).

BSPM constructed at 3/16 of the interval from the J point to T offset (mid ST-segment) revealed that the maxima in pts tended to be greater and shifted downward and to the right compared to N, but were not influenced by the Int. Similarly, the Int did not statistically alter total ST amplitude at this time point or the percent of total map area bounded by the 0.1 mV isopotential line. These data suggest that ischemia is an unlikely cause of persistent STE. Moreover, iso-integral plots (integrated area of the first 6/16 of the QRS complex and of the ST-T segment) in pts revealed a repolarization maximum (STE) reliably superimposed on a QRS minimum (Q wave). Since Q waves usually indicate scar tissue, it seems likely that the STE reflects unopposed posterior wall forces rather than a border zone of ischemic cells.

VENTRICULAR TACHYCARDIA: RAPID ANALYSIS OF EPICARDIAL ACTIVATION SEQUENCES

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Surgical intervention may prove to be the necessary approach to life-threatening ventricular arrhythmias shown to be unresponsive to medical therapy. A method has been developed in which it is possible to quickly evaluate epicardial activation sequences (EAS) during these rapid and often unstable rhythms. This technique makes it possible to determine global EAS during one beat of ventricular tachycardia (VT). 7 dogs were studied 4-8 weeks after coronary artery ligation. In all 7 dogs the infarcted area was extensively explored electrophysiologically with epicardial and transmural electrodes. In 2 dogs it was possible to evoke reproducible episodes of VT with programmed premature stimuli. A mesh sock containing 26 bipolar electrodes was fitted around the ventricles to record local electrograms simultaneously. Data from the sock electrode during VT were stored on a 32 channel FM tape recorder and converted to digital form for generation of isochronous maps by a PDP 11/34 computer. The earliest area of EAS was quickly identified from the computer-drawn isochronous maps. The early area was explored further during VT with a 25 unipolar point grid electrode (35 mm x 35 mm). 5 needles, each containing 5 recording sites along its shaft, were plunged into the myocardium around the earliest area of EAS to determine subendocardial activation patterns during VT. Correlation of sock, grid and needle electrode data revealed a unifocal site of origin of each episode of VT. This technique provides a rapid display of EAS in a few minutes and should prove useful in intraoperative localization and treatment of drug-resistant VT.

ASSESSMENT OF THE VALUE OF ECG SIGNS FOR MYOCARDIAL INFARCTION IN LEFT BUNDLE BRANCH BLOCK BY THALLIUM-201.

Frans Wackers,MD,K.I.Lie,MD,George David,MD,Dirk Durrer, MD,FACC and Hein Wellens,MD,FACC. Depts. of Cardiology and Nuclear Medicine,Wilhelmina Gasthuis, Amsterdam.

In 96 consecutive patients (pts) with left bundle branch block (LBBB) various ECG signs for myocardial infarction (MI) were analyzed for the sensitivity (SE) specificity (SP) and predictive accuracy (PA). No MI was present in 33 pts, 15 had previous (P) MI, 48 pts had acute (A) MI. All pts had Thallium-201 scintiscans (SC). All pts with no MI had normal SC, all pts with PMI or AMI had defects on SC. The ECG's were read by 3 observers, without clinical or SC data for the presence of:notch ascending limb S V_{3-4}(Cabrera);notch ascending limb R I-avL-V_6(Chapman); initial notching QRS (IN);RS in V_6(RS); ST elevation (ST↑); RV_1/QV_6; abnormal Q (AbnQ) and positive T waves (PosT). ECG changes were present in 75% of the pts with AMI. The interobserver disagreement on ECG was considerable. Good agreement existed only for ST↑:95%. The following results are average values of 3 observers for identifying AMI in LBBB:

ECG sign:	SE	SP	PA	ECG sign:	SE	SP	PA
Cabrera (CA)	24%	88%	80%	ST↑	53%	95%	95%
Chapman (CH)	19%	84%	72%	RV_1/QV_6	7%	98%	87%
IN	32%	76%	67%	AbnQ	23%	94%	87%
RS	6%	91%	55%	PosT	8%	63%	55%

Correlation with various locations of AMI did not change the values significantly, except for anteroseptal (AS) AMI. In ASAMI for CA SE=43%,SP=85%, and PA=68%;for RV_1/QV_6SE=20%,SP=100%,PA=100%. When PMI was included, except for ST↑ comparable values were obtained. CONCLUSION:1) ECG signs for AMI in LBBB have reasonable SP and PA, but low SE. The most sensitive sign is concordant ST↑. 2)When MI is suspected in pts with LBBB, Thallium-201 SC is the diagnostic method of choice.

CONTINUOUS UNIPOLAR STRENGTH-INTERVAL CURVES AND CONDUCTION TIMES DURING MYOCARDIAL ISCHEMIA AND REPERFUSION

Herbert J. Levine, MD, FACC; Boaz Avitall, PhD; Stephen G. Pauker, MD, FACC; Shapur Naimi, MD, FACC, Tufts New England Medical Center, Boston, Massachusetts

A computer program was developed to generate alternating anodal and cathodal or continuous anodal strength-interval curves (SIC) during and following 15 min. coronary ligations in 14 anesthetized dogs atrially paced at 2.5 Hz. SIC's were generated every 45-120 sec. and simultaneous conduction times (CT) determined. Within 1-2 min. of ligation, anodal mid-curve and late diastolic thresholds (TH) fell sharply, while cathodal TH fell slightly or changed little. After 5 min. of ligation, anodal TH remained low, cathodal TH rose and CT's prolonged markedly. At 10-15 min. of ligation, if ischemic zone was small, anodal TH were low, often approaching cathodal, and CT returned towards control. If ischemic zone was large, unipolar TH's and CT's rose in late ligation. Throughout ligation, the falling limb of the SIC shifted progressively to the left, indicating shorter refractory periods. Following abrupt reperfusion, anodal phase 3 dips, often wider and deeper than control, promptly reappeared (1-2 min.); refractory periods approached control, and superconductivity was noted. By 3-5 min. of reperfusion, refractory periods were longer than control and CT's were prolonged. Thus, vulnerability to arrhythmias of early (5 min.) ligation is characterized by low anodal mid-curve and late diastolic TH's, short refractory periods, and long CT's, favoring re-entry. Vulnerability to arrhythmias of early reperfusion is characterized by low dip TH's and short CT's. Finally, directional changes in anodal excitability correlate better than cathodal with vulnerability to arrhythmias of ligation and reperfusion.

RELATIONSHIP OF REGIONAL MYOCARDIAL BLOOD FLOW TO THE ELECTRICAL STABILITY OF TRANSMURAL AND SUBENDOCARDIAL ISCHEMIC MYOCARDIUM

Michael Cleman, P. Jacob Varghese and Bertram Pitt, Johns Hopkins Hospital, Baltimore, Maryland.

This study was performed to determine the role of regional myocardial blood flow (MBF) (ml/min/100 gm) in predicting electrical stability, as measured by ventricular fibrillation threshold (VFT), of subendocardial (SI) and transmural (TI) ischemic myocardium. In 12 open chested dogs VFT and MBF, as measured by 10u radioactive microspheres, were determined in the subendocardium (En) and subepicardium (Ep) of the region supplied by the left anterior descending (LAD) and left circumflex (LCX) coronary arteries during control conditions (C), following SI created by partial stenosis, and TI produced by occlusion of the LAD. VFT was determined by delivering a train of impulses after every 12th paced beat through bipolar hook electrodes placed in each region. Using a constant current source, the intensity of the train was increased by 1ma until ventricular fibrillation occurred.

	LAD-En		LAD-Ep		LCX-En		LCX-Ep	
	VFT	MBF	VFT	MBF	VFT	MBF	VFT	MBF
C	16	80	16	81	19	80	16	78
SI	5*	44*	12	80	20	80	20	85
TI	5*+	1.5*+	5*	7.5*+	8*+	78	8*+	82

*p<.05 compared to C, +p<.05 compared to SI

During SI a decline in MBF predicts regional electrical instability while with regional TI the entire heart becomes electrically unstable.

RELATIONSHIPS BETWEEN ELECTRICAL LOSS AND MUSCLE MASS LOSS IN MYOCARDIAL INFARCTION

Nancy C. Flowers, MD, FACC; R. Chris Hand; Leo G. Horan, MD, FACC; M.R. Sridharan, MD, University of Louisville, Louisville, Kentucky

Much attention has been directed toward enzymatic and electrical means of estimating the size of myocardial infarction. However, no previous comparisons have been reported on simultaneously acquired data from multiple lead body surface maps, the more simply obtained 3 vectorcardiographic orthogonal leads (VCG) and precordial electrocardiographic (ECG) grid systems.
Experimental myocardial infarctions have been produced in ten dogs utilizing a technique of coronary occlusion by a catheter-implanted bead in a completely closed chest (thus avoiding changes in the electrical properties of the thorax). Simultaneously acquired body surface map data, VCG data and ECG grid data were obtained before and 7 days following infarction. The post infarction electrical data were subtracted from the preinfarction. The resulting difference data for all three graphic systems were examined both for instantaneous and cumulative values during ventricular activation. Infarct volume was measured by serial section of the ventricular mass. The best correlation between instantaneous potential at msec 17 ($r = .88$) for difference map data dropped as the cumulative difference potential between 1 and 31 msec was obtained ($r = .85$). But the VCG correlation for msec 18 ($r = .70$) improved with cumulative spread ($r = .80$). Precordial grid data ran a poor third (maximum $r = .48$). We concluded that the difference map was superior in both localizing and estimating size of myocardial infarction though the VCG did well in estimating size. Caution must be exercised with any of the techniques to avoid inclusion of late activation data, which may contain variable effects of delayed conduction or block.

THURSDAY, MARCH 9, 1978
AM
EXERCISE TESTING AND CARDIAC REHABILITATION
8:30 to 12:00

EFFECT OF ADDITIONAL WARMUP ON STANDARD TREADMILL RESPONSE.

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Eleven normal males, mean age = 32 years, underwent treadmill exercise testing (TT) using standard (S) and modified (M) Bruce treadmill protocols on separate days. All subjects had at least 1 TT prior to this study. M Bruce protocol is identical to the S protocol except for an additional 3 minute warmup (1.7 mph, 5% grade). A randomized testing sequence was used to test the hypothesis that, excluding the warmup, the response to both protocols are similar. Care was taken to assure that subjects were exercised to the same level of maximal fatigue on both M and S TT. The mean duration for M (excluding the 3 minute warmup stage) was greater than S (M = 651 $\pm$ 115 seconds, S = 631 $\pm$ 121 seconds, $p<.03$). Increased duration for M occurred regardless of testing sequence. Peak heart rate (HR) for M was 187 $\pm$ 11 vs. 183 $\pm$ 14 for S. Peak pressure-rate product (PRP) (HR x systolic pressure x 10^{-2}) was 378 $\pm$ 47 for M vs. 357 $\pm$ 58 for S, $p<.01$. Four minutes of exercise were required during M to approach a PRP similar to that attained with S in one minute (M = 154 $\pm$ 25 at minute 4, S = 157 $\pm$ 29 at minute 1). To test the hypothesis that these differences are due to greater oxygen debt created by S compared to M peripheral venous lactate levels were obtained at the end of stage II in 3 subjects. Comparing rest vs. stage II values there was a marked increase with S (10.7 vs. 28.7mg/100ml). During M protocol there was no difference between rest vs. stage II values (19.5 vs. 17.9mg/100ml). We conclude that the responses to the 2 protocols, corrected for the longer warmup period of the M protocol are different. The differences (>TT duration, hemodynamic responses, and lower lactates) are likely attributable to a longer warmup period and less anaerobic metabolism with M compared to S.

LACK OF ACUTE EFFECTS OF NITRATES ON EXERCISE CAPACITY IN CONGESTIVE HEART FAILURE

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Vasodilators acutely improve resting hemodynamics in congestive heart failure (CHF) but their immediate effects on the response to exercise (E), also a vasodilator stimulus, in CHF are not known. We performed bicycle E to symptomatic maximum in 8 patients with class II-III CHF before and 1.5 hrs after 40 mg of oral isosorbide dinitrate (IS). Expired air was collected for oxygen consumption (VO) and cardiac index (CI by CO_2 rebreathing), and pulmonary wedge pressure (PWP) was monitored by Swan-Ganz catheter. Resting hemodynamics were unchanged after IS except for a fall in PWP to 15.4 ± 2.7 (SEM) from 23.6 ± 3.3 mm Hg ($p<0.001$). Exercise duration was unchanged by IS (9.5 ± 1.8 vs 9.6 ± 1.8 min). VO at maximum E was unchanged by IS (15.5 ± 2.2 ml/kg/min before and 15.3 ± 1.7 ml/kg/min after) as well as maximal CI (4.21 ± 0.49 L/min/m^2 vs 4.24 ± 0.47 L/min/m^2). Heart rate and mean arterial pressure at peak E were unchanged by IS while systemic vascular resistance averaged 14.7 ± 2.3 units before and 14.3 ± 2.7 units after IS. PWP at peak E was reduced insignificantly from 40.4 ± 2.4 mm Hg to 36.0 ± 2.9 mm Hg after IS. In conclusion, nitrates which may chronically increase E tolerance in CHF do not acutely improve E capacity or alter E hemodynamics in CHF, perhaps because they do not acutely augment the vasodilation induced by E itself.

EXERCISE-INDUCED HYPOTENSION IN THE YEAR FOLLOWING MYOCARDIAL INFARCTION.

Dennis Davidson MD, Robert DeBusk MD, FACC, Stanford Univ. School of Medicine, Stanford, CA.

To evaluate the prevalence and mechanisms of exercise-induced hypotension (EHP) following myocardial infarction (MI), 150 men, mean age 54, had treadmill testing (TM) at 3, 7, 11, 26 and 52 weeks post-MI. EHP, always an endpoint in exercise testing, was defined as a fall of ≥10 mm Hg in indirectly measured systolic blood pressure (SBP) from the peak exercise value. There was no significant difference between anterior MI (AMI) and inferior MI (IMI) patients (pts) in the incidence of pre-MI angina, extent of infarction, in-hospital hypotension or post-MI TM maximum SBP, work load and ST depression.

EHP occurred in 11-19% of pts at each testing period. Forty-seven of 150 (31%) pts had 1 or more EHP episodes: 21 of 41 (51%) with AMI, 20 of 95 (20%) with IMI and 6 of 14 (43%) with non-transmural MI. None developed heart failure. The incidence of EHP remained constant throughout the year. There was no correlation of MI site with TM maximum work load, SBP or EHP occurrence at any of the 5 testing periods. At 3 and 7 weeks, IMI pts had EHP at significantly lower heart rates (HR) (118, 120) than AMI pts (132,150). Max. work load and the incidence of TM ischemia were equal for EHP and non-EHP pts. These data suggest a different mechanism of EHP for AMI and IMI pts, particularly early post-MI.

During a mean followup of 2 yrs, 4 of 41 AMI pts and 5 of 95 IMI pts had another MI. Of the 95 IMI pts, 2 of 20 EHP and 3 of 75 non-EHP pts had another MI; 1 of 20 EHP and 3 of 75 non-EHP pts had sudden death. No AMI pt had sudden death.

CONCLUSION: Compared to AMI pts, IMI pts developed EHP less frequently, but at lower heart rates during 3 and 7 week post-MI TM. EHP was not correlated with ischemia or with prognosis.

EXERCISE TESTING IN MITRAL VALVE PROLAPSE

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Abnormal repolarization responses to treadmill exercise testing (TM) have been noted in patients (pts) with mitral valve prolapse (MVP); yet the true frequency of this association is unknown. During aeromedical evaluation since 1972, 23 aircrew members (all male, mean age 37 ± 7 years) were found to have MVP (without evidence of other cardiovascular disease), as defined by the presence of typical findings in at least two of the following categories: auscultation-phonocardiography (AP - 20 pts), echocardiography (22 pts), and left ventricular cineangiography (8 pts). Twenty of the patients were asymptomatic, including the 3 patients without AP. At least one maximal TM (modified Balke protocol, monitoring orthogonal leads X, Y, and Z and a modified lead V_5) was available for review in each patient. An abnormal repolarization response was defined as at least 1 mm of horizontal or downsloping ST segment depression. Of the 23 patients, 7 had at least one abnormal TM (30%). Six of these 7 patients were asymptomatic, and 3 were without AP. Six underwent diagnostic catheterization including coronary arteriography, and all were free of coronary artery disease (CAD). No specific pattern of lead positivity was noted.

In conclusion, MVP appears to be frequently associated with abnormal TM in the absence of CAD. In addition, MVP should be considered in the differential diagnosis of an abnormal TM even in the absence of symptoms and typical auscultatory abnormalities of MVP.

EFFECT OF EXERCISE ON LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH CORONARY DISEASE

John K. Frischknecht, MD; Peter P. Steele, MD; Dennis L. Kirch, MSEE; Robert A. Vogel, MD, Denver Veterans Administration Hospital, Denver, Colorado.

Left ventricular (LV), ejection fraction (EF) was measured at rest and during graded supine bicycle exercise in 31 men with arteriographically defined coronary disease (CAD) and in 15 normal men. LVEF was calculated from a LV time vs activity curve (collimated dual crystal scintillation probe; first transit; ^{99m}Technetium) as the fractional fall in LV count-rate divided by the background-corrected LV end-diastolic count-rate. In normal men LVEF at rest averaged .59 ± .06 (± SD) and during exercise averaged .72 ± .08. The dual crystal probe measurement of LVEF correlated (r=0.89) with LVEF computed from single plane (RAO) contrast LV cineangiogram (N=25). Average LVEF failed to increase with exercise in men with CAD (.55 ± .03 to .57 ± .03; AVE ± SEM; NS). In 17 men with CAD who had ST depression (> 1 mm) during exercise, LVEF either failed to increase (> .05) or decreased in all (.55 ± .04 to .49 ± .03; NS); whereas in 14 without ST depression, LVEF increased in 10 (71%) and failed to increase in 4 (29%) (.54 ± .04 to .66 ± .04; $P<0.05$). Of 10 men with CAD, normal resting LVEF (> .46) and without exercise ST depression, 4 (40%) had an abnormal exercise LVEF and 6 (60%) had an increase of LVEF with exercise. Results suggest that LVEF normally increases during exercise and that men with CAD and exercise ST depression have an abnormal LVEF response to exercise. An abnormal exercise LVEF was frequently observed in men with CAD who did not have ST depression, suggesting that measurement of exercise LVEF may increase the sensitivity of exercise testing.

IMPORTANCE OF ASYNERGY IN THE EXERCISE ELECTROCARDIOGRAPHIC RESPONSE OF PATIENTS WITH ANGINA PECTORIS AND CORONARY DISEASE

Michael D. Busky, MD; Michael S. Feldman, MD, FACC; Monty M. Bodenheimer, MD, FACC; Vidya S. Banka, MD; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

The diffuseness and severity of coronary obstructive disease has been shown to significantly affect the appearance and severity of exercise induced ST segment depression. However, little is known of the relationship between the ST segment response to exercise and ventricular performance. Thus, 55 patients with angina and coronary artery disease (≥75% obstruction of one or more major vessels) underwent maximal treadmill stress, and the relationship between ST depression with exercise (positive ST), asynergy and the number of involved vessels was evaluated. None had clinical heart failure. Thirty-six had positive and 19 negative ST responses. Twenty-one of the 25 patients with 3 vessel disease had positive ST's while 13 of 19 with 2 vessel and one of 11 with 1 vessel disease had positive ST's ($p<.001$). However, of those with 3 vessel disease, 20 of 21 with positive ST's had asynergy while 1 of the 4 with negative ST's had asynergy ($p<.025$). In the 2 vessel disease group, all 13 with positive ST's had asynergy while 4 of the 6 with negative ST's had no asynergy ($p<.001$). When asynergy was evaluated independently, only 5 of the 18 (27%) with no asynergy had positive ST's while 28 of 37 (76%) with asynergy had positive ST's ($p<.001$). Of the 13 with no asynergy and negative ST's, 6 had 1 vessel, 3 had 2 vessel and 4 had 3 vessel disease. Conversely, of the 33 with both 2 or 3 vessel involvement and asynergy, only 3 had negative ST's. Thus, in addition to the number of obstructed vessels, asynergy appears to be an important additional factor in the ST segment response to exercise.

EXERCISE TRAINING SOON AFTER MYOCARDIAL INFARCTION.

Nancy Houston RN, William Haskell PhD, Robert DeBusk MD FACC, Cardiology Div., Stanford Medical School, Stanford, CA. Gary Fry MD, YMCArdiac Therapy Program, Palo Alto, CA.

To assess the effect of exercise training (ET) on functional capacity (FC) soon after myocardial infarction (MI) 34 patients (pts) mean age 52, matched for clinical severity of MI and post-MI physical activity level, were randomly assigned to control group, home ET or gym ET. No significant intergroup differences in age or severity of infarction were noted. Training heart rates for pts receiving home or gym ET were 60-80% of peak values recorded during symptom-limited treadmill tests at 3 weeks post MI. Both exercise groups performed 3 1-hour ET sessions per week for 8 weeks. Pts performing home ET used heart rate monitors to regulate the level of effort during stationary cycling and to transmit electrocardiograms via telephone during ET sessions. Treadmill tests were repeated on all pts at 11 weeks post-MI. FC was expressed as multiples of resting oxygen consumption (estimated) or METs. RESULTS:

	3 weeks		11 weeks		
	Max HR	Max METs	Max HR	Max METs	ΔMETs
Control n=13	134±17	7.1±1.4	150±20	9.9±1.6	2.8*
Home ET n=7	151±19	7.6±1.3	156±24	10.2±1.8	2.6*
Gym ET n=14	139±23	7.3±2.1	149±22	10.5±2.1	3.2*
Intergroup differences	NS	NS	NS	NS	*3vs11 wk P< 0.01

CONCLUSIONS: 1) Individualized physical exercise training commencing as soon as 3 weeks post-MI appears to be safe in well selected and monitored patients. 2) A substantial increase in FC noted between 3-11 weeks post-MI was not further augmented by exercise training within this population.

EXERCISE-INDUCED REDUCTION IN MYOCARDIAL INFARCT SIZE AFTER CORONARY ARTERY OCCLUSION IN THE RAT. A PRELIMINARY REPORT.

Caryl L. McElroy; Sally A. Gissen, BS; Michael C. Fishbein, MD, Dept. of Pathology, Peter Bent Brigham Hospital and the Harvard Medical School, Boston, MA.

Chronic exercise(E) has been thought to be beneficial to the cardiovascular system by increasing energy production and utilization, improving myocardial contractility and increasing myocardial vascularity; whether or not any of these effects are beneficial to ischemic myocardium is uncertain. In this study, rats were forced to swim 1 hr/day, 5 days/wk for 5 wks. They were sacrificed and the myocardial capillary bed was perfused with carbon black. Using a calibrated eyepiece grid, histologic sections of heart were examined to determine capillary/fiber ratios (C/F) and myocardial fiber diameter. C/F was increased by 30% in E rats [0.87±0.06(mean±S.E.)(n=4 rats)] when compared with sedentary controls(C) [0.67±0.04(n=4 rats),$p<0.05$]. This training effect occurred in the absence of hypertrophy since there were no differences in ventricular weight (1.21±0.04mgs in E rats vs 1.16±0.03mgs in C rats,NS) or in fiber diameter (13.0±0.2μ in E rats vs 13.1 ±0.2μ in C rats,NS) in the 2 groups. An additional 27 E rats and 25 C rats underwent left coronary artery occlusion and were sacrificed 48 hrs later. Myocardial infarct size was measured by planimetry of histologic sections of serial slices of left ventricle(LV). In the 27 E rats, 21.5±1.9% of the LV was infarcted compared with 31.3±2.6% in the 25 C rats($p<0.005$). Thus, infarct size was reduced by 30% in E rats. In the rat, exercise results in a reduction of myocardial infarct size after coronary artery occlusion which, at least in part, may be related to increased myocardial vascularity.

PREDICTIVE VALUE AND SAFETY OF LOW LEVEL EXERCISE TOLERANCE TESTING EARLY AFTER ACUTE MYOCARDIAL INFARCTION

Pierre Thêroux, MD; Christine Halphen, MD; David D.Waters, MD, FACC; Henry F. Mizgala, MD, FACC, Montreal Heart Institute, Montreal, Quebec

Exercise testing is highly predictive of subsequent coronary events and mortality in most populations. Accordingly, graded exercise tests (ETs) were done in 125 consecutive pts (mean age 52) 12 days (7-24) after acute myocardial infarction to determine in this setting its safety and prognostic value. Pts with a physical handicap, overt heart failure, angina within 72 hours or aged >70 years were excluded. End-points were 70% of the maximal age predicted heart rate, 5 metabolic equivalents, ST depression ≥1.5 mm, typical angina, incapacitating fatigue or the appearance of a serious arrhythmia. The development of 1.5 mm of horizontal or downsloping ST depression or typical angina were criteria for a positive test (+ET). Resting ECG and CPK-MB done before and at 6 and 12 hours after ET were unchanged. One pt had severe chest pain 24 hours post ET without objective evidence of re-infarction.

22 pts had ventricular extrasystoles and an additional 2 had salvos. 46% of pts with ventricular arrhythmias (VAs) had ST depression but only 19% of those without VAs had ST depression ($p<0.02$). Overall 46 pts had +ETs and 69 -ETs. During the next 3 to 16 (mean 10) months, coronary events occurred in 25 pts, 13 of whom had had -ETs (NS). These events were unstable angina in 6 (1 with+ET), re-infarction in 14 (5 with+ETs) and death in 10 (3 with+ETs). 56% of pts with +ETs had subsequent angina at 3 months compared to 31% of those with -ETs ($p<0.02$).

We conclude that low level ET soon after myocardial infarction appears safe. VAs correlate with ST depression in this setting, suggesting that both may be caused by ischemia. +ETs predict subsequent angina but not early coronary events or death.

EXERCISE INDUCED DECREASES IN PLATELET AGGREGATION: COMPARISON OF NORMALS AND CORONARY PATIENTS SHOWING SIMILAR PHYSICAL ACTIVITY RELATED EFFECTS

James Joye, MD; Anthony N. DeMaria, MD, FACC; John Giddens; Roy Kaku, MD; Ezra A, Amsterdam, MD, FACC; Dean T. Mason, MD, FACC; Garrett Lee, MD, University of California, Davis, California

Although exercise alters blood coagulation, no data are available regarding exercise effects on platelet aggregation (PA). Thus PA studies were performed on eight coronary patients (CAD) and 12 normal subjects. All underwent multistage treadmill exercise (MTE) and PA was measured at 3 minute (min) intervals, at termination, and 10 min after MTE using $4x10^{-5}$ adenosine disphosphate stimulation after normalization of platelet count. Nineteen individuals completed 3 min MTE and manifested reduction in PA from 56.2 to 48.0%, p<.001. Sixteen exercised 6 min and PA decreased 54.9 to 46.4%, p<.01. Nine completed 9 min MTE and PA decreased 52.2 to 43.6%, p<.01. Ten min post-MTE PA remained reduced 57.2 to 49.8, p<.05. Decreased PA was observed in both CAD and normal subjects, and reduction of PA was identical at exercise levels of equivalent maximal percentage. These data indicate exercise produces decrease in PA related to level of exertion. No rebound of PA was observed immediate post-MTE. These observations demonstrate that exercise-induced reduction in platelet aggregation is similar in normals and coronary patients.

IN VIVO DEMONSTRATION OF THE FRANK-STARLING MECHANISM IN THE HUMAN DENERVATED HEART

Stephen E. Pope, MD; Neil B. Ingels Jr., PhD; George T. Daughters II, PhD; John S. Schroeder, MD, FACC. Cardiology Division, Stanford Medical Center and Palo Alto Medical Research Foundation, Palo Alto, California

The denervated human heart provides an ideal clinical model for the in vivo description of the Frank-Starling mechanism, unmodified by autonomic influences. Six long-term cardiac transplant recipients were studied by computer-assisted fluoroscopic analysis of radiopaque tantalum markers located in the left ventricular (LV) mid-wall. This permitted sequential quantitation of routine hemodynamic recordings and LV volumes as a direct measure of mid-wall fiber length changes. Acute volume loading was achieved by sudden leg elevation from the supine position.

	Control	Leg Elevation	%Δ	P Value
HR(beats/min)	100±4	101±4	1%	NS
LVEDV(ml)	91±6	101±6	+12%	<.01
SV(ml)	42±2	50±2	+20%	<.001
CO(L/min)	4.2±.3	5.1±.4	+19%	<.01
VCF(circ/sec)	.70±.04	.84±.06	+20%	<.05

LVEDV = left ventricular end-diastolic volume; SV = stroke volume; CO = cardiac output; VCF = velocity of circumferential fiber shortening.

We conclude that acute volume loading of the denervated heart (with 12% increase in EDV) results in a substantial (20%) rise in CO and VCF, reflecting augmented contractility and LV work, independent of neurally-mediated changes in HR or LV contractility.

COMPARATIVE BENEFITS OF EXERCISE TRAINING IN GRAFTED AND UNGRAFTED CORONARY PATIENTS

Andrew C. Drakonakis, MD, FACC; Allan M. Ross, MD, FACC, VA Hospital, West Haven, and Yale Univ., New Haven, Ct.

Nineteen vein bypass operated (OP) and 30 unoperated coronary disease (CD) patients (pts) had 35-40 thrice weekly heart rate (HR) monitored sessions of exercise training (TR), 30 min. each, at 80-85% of max HR determined by 2 pre TR tests. Treadmill retesting was done at 6 and 12 wks of TR. HR, systolic pressure (SP) and their product (HRSP) were analyzed at rest, at two levels corresponding to 1/2 and 2/3 of initial work capacity (WC) in mets, and at max effort. In both groups the WC increased significantly (*=p<.05 paired t vs initial value, table & text) after TR; in OP by 23%* at 6 and by 30%* at 12 wks; in CD by 21%* and 24%*. HR, SP and HRSP (see table) did not change at rest or max effort but decreased significantly at submaximal levels. Thus the ratios of HR, SP and HRSP over WC decreased at all levels of exercise.

	HRSP$x10^{-3}$				SP (mm Hg)				HEART RATE			
	INITIAL		12 WEEK		INITIAL		12 WEEK		INITIAL		12 WEEK	
	OP	CD	OP	CD	OP	CD	OP	CD	OP	CD	OP	CD
Rest	10	9	9	9	124	127	124	120	79	73	75	71
1/2 max	16	14	13*	12*	146	139	130*	127*	108	101	99*	94*
2/3 max	20	17	17*	15*	159	150	146*	137*	126	114	113*	106*
Max	24	21	25	21	166	159	171	154	141	128	145	132

Of 18 CD pts with angina limited stress testing, 3 became angina free. The remainder improved their WC by 22%*. For 9 OP angina pts, WC increased by 33%*. CONCLUSIONS: There is no difference in response to TR between operated and non-operated pts. For both groups max HRSP was unchanged after TR whereas max WC increased, and the ratios of HR, SP and HRSP over submax and max work loads decreased similarly.

THURSDAY, MARCH 9, 1978
AM
HYPERTROPHIC CARDIOMYOPATHY AND THE MITRAL PROLAPSE SYNDROME
8:30 to 12:00

OBJECTIVE ANGIOGRAPHIC CRITERIA FOR THE DIAGNOSIS OF MITRAL VALVE PROLAPSE. Eldon R. Smith, MD; David B. Fraser, MD; Amar S. Kapoor, MD; Henry Gewirtz, MD; and Rosalind MacDonald. Dalhousie University, Halifax, N.S. Canada.

Although angiography (angio) generally has been accepted as the diagnostic standard for mitral valve prolapse (MVP), recent reports question the specificity of angio criteria. Thus in a recent study from our laboratory, 43% of unselected patients (pts) undergoing angio had end-systolic bulging of the posterior mitral leaflet. Since most of the apparent "false-positives" resulted from bulging of the postero-medial scallop (PMS), we have attempted to quantitate the angio assessment of this scallop. Using end-systolic outlines of the 30 degree right anterior oblique angio, the best criterion identified was the perpendicular distance which the PMS extends from a line connecting the posterior aortic root - left ventricular (LV) junction to the fornix of the mitral valve - LV inferior wall, normalized for LV minor axis. Of 17 pts with the click-murmur syndrome and typical echocardiographic (echo) features of MVP, all had a PMS length index (PMSLI) ≥0.27 (range 0.27 to 0.68; mean 0.39). This index has been assessed in a prospectively studied series of 104 pts with clinical, phono, echo and angio data in all. By subjective assessment of angio, 44 (39.6%) had MVP involving the PMS, a finding in close agreement with the previous study. Of 94 pts in whom the PMSLI could be measured, only 17 (18%) had values ≥0.27 and 8 of these had phono and/or echo features of MVP. One pt, with a mid-systolic click but normal echo, had a PMSLI of 0.26.

We conclude that the specificity of angio diagnosis of MVP (involving the PMS) can be considerably improved by objective measure, with a PMSLI <0.27 probably reflecting normal variation in the LV end-systolic configuration.

MITRAL VALVE PROLAPSE SYNDROME AND RECURRENT VENTRICULAR TACHYARRHYTHMIAS: A MALIGNANT VARIANT REFRACTORY TO CONVENTIONAL DRUG THERAPY. Jeanne Wei, M.D., Bernadine H. Bulkley, M.D., F.A.C.C., Alan H. Schaeffer, M.D., H. Leon Greene, M.D., F.A.C.C., Philip R. Reid, M.D., F.A.C.C. The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Of 60 patients referred specifically for management of refractory ventricular tachyarrhythmias (VT) with the new antiarrhythmic agent aprindine, 10 patients (17%) had a midsystolic click and/or a late systolic murmur, and mitral valve prolapse (MVP) demonstrated by left ventricular cineangiogram or echocardiogram. They ranged in age from 19 to 70 years, (average 47), and 7 were women. All had symptoms referrable to arrhythmias, and 8 had chest pain. All 10 had recurrent VT, while 4 had a history of ventricular fibrillation. In 9 patients the chest x-ray was normal, and 8 had normal coronary arteriograms. In addition to ventricular arrhythmias, the resting electrocardiograms showed widened QRS complexes in 2, non-specific ST-T wave changes in 9, and prolonged QT intervals in 5.

Of the standard anti-arrhythmic agents, 9 were refractory to propranolol, with 3 in combination with quinidine, 3 in combination with procainamide and quinidine, and 2 in combination with phenytoin; 1 patient was refractory to the combination of quinidine, procainamide, atropine, phenytoin, and disopyramide. All showed improvement with aprindine therapy. The results show that: 1) refractory malignant ventricular arrhythmias may be associated with MVP syndrome; 2) MVP patients accounted for a significant percentage of those patients referred with recurrent VT refractory to standard anti-arrhythmic therapy; 3) in patients with unexplained ventricular arrhythmias, MVP should be considered, and 4) aprindine may be effective for VT associated with MVP.

ABNORMAL MYOCARDIAL PERFUSION DEFECTS IN PATIENTS WITH MITRAL VALVE PROLAPSE AND NORMAL CORONARY ARTERIES Howard M. Staniloff, MD, Victor F. Huckell, MD, John E. Morch, MD, Andrew J. Buda, MD, David H. Feiglin, MD, E. Douglas Wigle, MD; Peter R. McLaughlin, MD, FACC, Toronto General Hospital, Toronto, Canada.

Thallium-201 (Tl-201) myocardial studies were done in 20 patients (pts), mean age 44 yrs, with angiographically documented mitral valve prolapse, normal coronary arteriograms and severe exertional chest pain. Stress electrocardiograms were positive in 4, non-interpretable (NI) (failure to reach target heart rate) in 7 and negative in 9 pts. Rest and exercise Tl-201 studies were analyzed by 3 independent observers. Of the 20 pts, 8 had perfusion defects at rest unchanged with exercise, 3 had new perfusion defects on exercise and 9 had normal Tl-201 studies at rest and exercise. There was no correlation between stress electrocardiograms and perfusion defects.

	Stress Electrocardiogram		
Tl-201	Positive	N.I.	Negative
Perfusion Defects	2	2	7
Normal	2	5	2

In patients with mitral valve prolapse and exertional chest pain randomly distributed perfusion defects are common suggesting areas of regional malperfusion and/or cellular dysfunction. New perfusion defects on exertion (3/20 pts) suggest ischemia as a cause of pain in some pts. The presence or absence of perfusion defects at rest or exercise in patients with mitral valve prolapse cannot be used to detect or exclude coronary artery disease.

A PROSPECTIVE STUDY OF MITRAL VALVE PROLAPSE IN YOUNG MEN. James A. Sbarbaro, M.D., David Mehlman, M.D., Louis Wu, M.D., Harold L. Brooks, M.D., F.A.C.C., University of Chicago, Chicago, Illinois.

Although the mitral valve prolapse (MVP) syndrome [MVP and/or systolic click-murmur (SC-M) with symptoms of chest pain and/or palpitations (SX)] is surprisingly common in young women, its incidence and clinical significance in young men has not been established. 100 healthy, randomly-selected male medical students were studied prospectively using a uniform evaluation sequence including history, ECG, multi-positional physical exam and phonocardiogram, and echocardiogram (ECHO). The study showed little relationship between ECHO-proven MVP and other clinical findings. Four had definite MVP on ECHO with no SX, SC-M or abnormal ECG; and two had SC-M with normal ECHO and ECG. 21/94 without MVP or SC-M had SX, compared with 0/4 in the MVP, and 1/2 in the SC-M groups. Thus, neither history, physical, nor ECG separated the 4 ECHO positive (+) subjects from the entire group. In the ECHO+ group, Holter monitoring and treadmill testing were normal, and no stress-induced perfusion defects during exercise myocardial scintigraphy with N-13 labeled amonia were present. We conclude that the incidence of MVP in young men is higher than previously reported; that these patients are rarely symptomatic; anc that MVP may be an incidental ECHO finding in this group. The absence of SC, dysrhythmias and perfusion defects further differentiates MVP in young men from that previously reported in other groups, and suggests that extensive evaluation is unwarranted in asymptomatic young men with MVP.

ABNORMAL AUTONOMIC FUNCTION IN PATIENTS WITH MITRAL VALVE PROLAPSE SYNDROME. F.A.Gaffney,M.D., W.G.Campbell,M.B., E.S.Karlsson, M.D., J.T.Willerson,M.D.,FACC, J.V.Nixon, M.D., C.G.Blomqvist, M.D.,FACC, University of Texas Health Science Center at Dallas, Dallas, Texas.

Certain features of mitral valve prolapse (MVP) suggest abnormal autonomic function. This was studied in 27 women; 14-echo/phono documented MVP, 13 normals (Nl), mean ages 29 and 28 respectively. At rest and during lower body negative pressure (LBNP) cardiac index (CI)-acetylene rebreathing technique, forearm flow (FF)- venous occlusion plethysmograph, calf volume changes (ΔCV)-Plethysmography, heart rate (HR), and blood pressure (BP) were measured.

LBNP mmHg		HR beat/min	CI $L/min/M^2$	BP mmHg	ΔCV %+	FF mm/min/100gm
0	MVP	72±3	3.5±.3	82±3	--	2.1±.2
	NL	68±2	3.6±.4	78±2	--	2.5±.2
-16	MVP	73±4	3.1±.3	83±4	.7±.1**	1.5±.2*
	NL	70±3	3.2±.3	79±2	1.2±.1	2.0±.1
-40	MVP	78±5	2.6±.3	86±3	2.1±.3**	1.3±.2
	NL	82±4	2.4±.2	75±2	3.2±.3	1.7±.2

(±SEM, *p<.05, **p<.01)

Changes in FF and ΔCV suggest abnormal α-adrenergic responsiveness in MVP patients.

Infused phenylephrine, raising $\overline{BP}$ 20-40mm caused less ↓$\overline{BP}$ in MVP than in Nl. (12±1,20±2, ΔHRmsec/$\overline{BP}$ΔmmHg; p<.01). The diving reflex-facial immersion in ice water caused less ↓HR in MVP than in Nl.(-37±4,-60±6 beats; p<.01).suggesting diminished vagal responsiveness.

The study suggests both sympathetic and parasympathetic abnormalities in MVP patients.

CONDUCTION ABNORMALITIES ASSOCIATED WITH MITRAL VALVE PROLAPSE IN PATIENTS WITH NORMAL CORONARY ARTERIES

Ronald R. Masden, MD; Daniel E. McMartin, MD; B.Y. Pathakjee, MD; Nancy C. Flowers, MD, FACC; University of Louisville, Louisville, Kentucky

In the past decade much attention has been focussed on the spectrum of mitral valve prolapse (MVP) syndromes. In certain case reports of the clinically diagnosed click-murmur syndrome, usually without angiographic confirmation of the prolapse, conduction disturbances have been sporadically observed. The present study, however, confined itself to 356 patients evaluated for chest pain and found to have normal cardiac catheterization data, including indices of ventricular function and coronary arteriography. These patients were further divided into 203, ages 20-70 years, (115 females and 88 males) with no ventriculographic evidence of MVP, and 153 patients, ages 18-71 years, (84 females and 69 males) clearly meeting ventriculographic criteria for MVP. These two groups were compared for the incidence of conduction defects. In the group without MVP one subject had right bundle branch block (RBBB) and one left bundle branch block (LBBB). No other conduction abnormalities were recorded. In the MVP group, 13 demonstrated multiple conduction system abnormalities including 6 with RBBB, one of whom also had left anterior hemiblock (LAHB) and two of whom also had left posterior hemiblock. A seventh had incomplete RBBB. Three had only LAHB. Two had LBBB and a third had LBBB alternating with RBBB. Five patients, on no drugs, demonstrated PR prolongation exceeding 210 msec. His bundle studies done on 2 of the patients with RBBB showed prolonged HV intervals of 97 and 73 msec respectively. We concluded that not only is there an increased incidence of rhythm disturbances in patients with MVP, but that even against the background of normal coronary arteries and normal hemodynamic function, there is an increased incidence of abnormalities of the His-Purkinje system as well.

VALUE OF NONINVASIVELY-INDUCED VENTRICULAR PREMATURE BEATS DURING ECHOCARDIOGRAPHIC AND PHONOCARDIOGRAPHIC ASSESSMENT OF PATIENTS WITH IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

Gerald H. Angoff, MD; John E. Markis, MD; Laurence J. Sloss, MD; Daniel Wistran, MD; Patricia C. Come, MD; Paul Zoll, MD; Peter F. Cohn, MD, FACC, Peter Bent Brigham Hospital and Beth Israel Hospital, Boston, Massachusetts.

Fifteen patients (pts) with idiopathic hypertrophic subaortic stenosis (IHSS) had ventricular premature beats (VPB) induced with a new external mechanical stimulator during noninvasive evaluation of left ventricular outflow tract obstruction. Ten pts were monitored with simultaneous echocardiography (ECHO) and phonocardiography and carotid pulse tracing (PHONO-CPT) while 5 were monitored by PHONO-CPT alone. Nine of the pts showed obstruction in the post-VPB beat as defined by appearance of the characteristic bifid carotid pulse, prolongation of the systolic ejection time (ET), and, where recorded, increase in systolic anterior motion of the mitral valve on ECHO. Six did not show obstruction. All 9 pts with obstruction had $\geq$ 20 msec prolongation of uncorrected ET in the post-VPB beat. Change in the uncorrected ET was +38±8 msec in these 9 pts as compared with -5±4 msec for the 6 not showing obstruction ($p<.01$). Six pts underwent cardiac catheterization: pts without obstruction during noninvasive evaluation had none at catheterization and pts with obstruction after noninvasively-induced VPB's demonstrated obstruction after provocative maneuvers during catheterization. No complications occurred and there were no pts in whom a VPB could not be induced noninvasively. These results indicate that the noninvasive induction of a VPB is a useful and easily performed procedure for both diagnosing and evaluating the dynamic left ventricular outflow tract obstruction of IHSS.

INDUCTION OF SARCOMEROGENESIS BY SYNCHRONOUS BIFOCAL VENTRICULAR PACING

Stephen Raskin, MD; Larry F. Lemanski, Ph.D.; Jacob Abouav, MD; Hyman W. Paley, MD; Mt. Zion Hospital, and VA Hospital, San Francisco, Ca.

Contraction induced linear stresses initiated by abnormal septal sympathetic innervation in dogs causes ultrastructural changes similar to those seen in idiopathic hypertrophic subaortic stenosis (IHSS). To isolate the role of an abnormal sequence of myocardial activation on sarcomerogenesis an altered contraction pattern was established in adult mongrel dogs. Following surgically induced heart block, nearly synchronous (0.1-0.5 msec delay) bifocal epicardial pacing was achieved with fixed rate and R-synchronous pacers. Augmented linear stresses between the electrode pairs was recorded by strain gauges at the time of implant. Sacrifice was performed at 20 weeks and morphological studies were obtained. All tissue from areas of stress submitted for electron microscopy revealed variable degrees of Z band thickening, thin filaments transversely attached to Z bands, dilata- of transverse tubules, increased autophagic vesicles, and mitochondrial swelling with bizarre branching cristae. These changes were not present in non-stress samples in the same dogs. The ultrastructural changes suggestive of sarcomerogenesis appear to be initiated by artificially altered myocardial activation pattern and may relate to the pathogenesis of IHSS in man.

IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS: LONG-TERM MEDICAL FOLLOW-UP

Roger G. Nissen, MD; Abdul J. Tajik, MD, FACC; Emilio R. Giuliani, MD, FACC; Robert O. Brandenburg, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Although propranolol (P) has been used in idiopathic hypertrophic subaortic stenosis (IHSS), little is known about the long-term follow-up of large groups of patients (pts) treated with various doses of P. One hundred nineteen pts (63 males, 56 females) more than 20 years old received P. Mean age was 58 years (range 23-79). Eleven pts were in NYHA Class I, 53 Class II, 51 Class III, and 4 Class IV at onset of P. Mean dose of P was 142 mg (range 40-640). Mean duration of follow-up was 40.9 mo (range 8-137). During this period, 51 pts (43%) symptomatically improved, 52 (44%) remained unchanged, and 16 (13%) deteriorated. Most improved were chest pain, dizziness, and palpitations; least improved was dyspnea on exertion. Of 119 pts, 10 (8%) eventually required surgical myotomy-myectomy because of either no improvement or deterioration of symptoms. Of the remaining 109 pts, 9 (8%) died (2 noncardiac deaths). Of the 7 cardiac deaths, 5 were sudden and occurred in pts with mean age of 61 years (range 28-78), all of whom were receiving P$\leq$160 mg daily. Of the 5 pts who died suddenly, 1 had right bundle branch block (RBBB), left axis deviation (LAD), and atrial fibrillation; one had RBBB and LAD; and one had atrial fibrillation without associated conduction disturbance. This study documented that, in a large group of pts, P in modest doses is effective in symptomatic improvement over long-term follow-up. However, sudden death was not prevented by P in dose $\leq$160 daily.

CARDIAC MUSCLE CELL DISORGANIZATION IN THE VENTRICULAR SEPTUM: EVIDENCE FROM QUANTITATIVE HISTOLOGY THAT IT IS A HIGHLY SENSITIVE MARKER OF HYPERTROPHIC CARDIOMYOPATHY

Barry J. Maron, MD: Stephen E. Epstein, MD, FACC: William C. Roberts, MD, FACC; NHLBI, Bethesda, Md.

The most characteristic histologic feature of hearts with hypertrophic cardiomyopathy (HCM) is the presence of numerous disorganized cardiac muscle cells (CMC) in the disproportionately thickened ventricular septum (VS). However, qualitatively, foci of disorganized CMC may be present in the VS of pts with other forms of cardiac disease. Hence, the present study was undertaken to determine for the first time, in quantitative terms, the extent of CMC disorganization in the VS of pts with HCM and in pts with concentric cardiac hypertrophy. Full thickness sections of VS were obtained at necropsy from 23 pts with HCM and from 107 pts with congenital or acquired cardiac disease. The relative area of myocardium involved by disorganized cells was determined quantitatively by video planimetry after 1000 fold magnification of the original tissue section on a positive photographic print. CMC was present in each pt with HCM and in 10(9%) of 107 pts with concentric hypertrophy ($p<0.01$). The area of tissue section involved by disorganization was significantly greater in pts with HCM (mean area = 50.0 $\pm$ 6.8%; in 20/23 pts >5% of myocardium was involved) than in pts with concentric hypertrophy (mean area = 1.0 $\pm$ 0.3%, in only 4/107 pts >5% of myocardium was involved; $p<0.01$). Hence, 1) CMC disorganization is uncommon in pts with concentric hypertrophy and when present usually involves <5% of the tissue section; 2) most pts with HCM show significant CMC disorganization (usually involving >15% of VS); 3) although CMC disorganization in VS, per se, is not pathognomonic of HCM, widespread distribution of CMC disorganization is a highly specific histologic marker for HCM.

PATHOPHYSIOLOGIC MECHANISM OF SEPTAL PERFORATOR ARTERY COMPRESSION.

John B. Kostis, MD, FACC; Abel E. Moreyra, MD; Narayanan Natarajan, MD, FACC; Maryhelen Hosler, RN; Peter T. Kuo, MD, FACC; Hadley L. Conn Jr., MD, FACC. CMDNJ-Rutgers Medical School, Piscataway, New Jersey.

Septal perforator coronary artery compression (systolic obliteration and diastolic reopacification, SPC) has been proposed as a marker of idiopathic hypertrophic subaortic stenosis (IHSS).
Review of 500 consecutive coronary arteriograms showed SPC in all patients (pts) with IHSS, (17 pts). However, SPC was also present in 4 of 10 pts with hypertrophic cardiomyopathy without asymmetric septal hypertrophy, in 11 of 18 pts with severe aortic stenosis (AS) (gradient >70mmHg) and in 3 of 17 pts with mild to moderate AS (gradient <70mmHg). SPC was also seen in 4 of 17 pts with myocardial bridge and in 12 of 40 pts with severe (>95%) stenosis of the proximal left anterior descending (LAD). SPC was not present in any of 58 pts with normal hearts and 323 pts with heart diseases other than those noted above.
SPC was most pronounced in pts with high intraventricular pressure and echocardiographic evidence of septal hypertrophy. For similar peak systolic gradients, across the aortic valve, ejection fractions and left ventricular end-diastolic pressures, SPC was more pronounced in IHSS than in AS ($P<0.01$).
Conclusions: 1) SPC is a finding frequently demonstrable but not specific of IHSS.
2) SPC depends on an interplay between altered intracoronary and intramyocardial pressures and is further facilitated by the abnormal septal anatomy of IHSS.

THURSDAY, MARCH 9, 1978
PM
ECHOCARDIOGRAPHY—II
1:45 to 4:00

ECHOCARDIOGRAPHIC ASSESSMENT OF THE LEFT VENTRICLE FOLLOWING MYOTOMY AND MYECTOMY FOR IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS (IHSS).

Walter H. Merrill, MD; Walter L. Henry, MD; Barry J. Maron, MD; Stephen E. Epstein, MD, FACC; Andrew G. Morrow, MD, NHLBI, Bethesda, Md.

Most pts who have had left ventricular myotomy and myectomy for IHSS at our institution have experienced marked symptomatic improvement but some have shown clinical deterioration at varying intervals postop. To evaluate this problem, echocardiograms were obtained before (62 pts) and 4 to 16 yrs following (27 pts) operation. Measurements included the left ventricular dimensions at end-diastole (LVDD) and end-systole (LVDS) from which percent fractional shortening of the base of the left ventricle was derived. Preop LVDD was <55mm and LVDS <36mm in all 62 pts. Fractional shortening was above the normal range (46-30%) in 23/62 (37%) pts and below normal in only 2/62 (3%). Thirty of 62 pts had repeat studies 6 mos following operation. Although all 30 pts had LVDD <55mm, 5/30 (17%) had a LVDS >36mm and fractional shortening <30%. In the 27 pts several yrs postop, 18 (67%) had a LVDD <55mm and a normal fractional shortening (mean follow-up 6.8 yrs), whereas 9 (33%) had a LVDD >55mm and a fractional shortening <30% (mean follow-up 7.3 yrs). Four of 18 (22%) pts with normal left ventricular dimensions and function have died or are symptomatic class III or IV, compared to 4 of 9 (44%) pts with a dilated, poorly contracting ventricle. Of 4 pts with a fractional shortening $\leq$20%, 3 are class III or IV. Thus, most pts undergoing myotomy-myectomy have good long-term symptomatic relief with maintenance of normal dimensions and function of the base of the left ventricle; however, there appears to be a subgroup of pts who develop left ventricular dilatation and decreased function following operation, presumably due to the underlying cardiomyopathy.

NONINVASIVE DETERMINATION OF THE LEFT VENTRICULAR FORCE-LENGTH RELATIONSHIP IN MAN

Nathaniel Reichek, MD; Philip Silverstone, BS; John Wilson, MD, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Existing noninvasive indices of left ventricular (LV) function are heavily influenced by preload and afterload and do not accurately reflect the intrinsic force-length (FL) relationship of the LV. Therefore, we have devised a simple, totally noninvasive method for estimation of peak systolic (PS) and end systolic (ES) instantaneous LV FL relationships using echograms of the aortic valve (AV) and LV combined with cuff blood pressure (BP). AV opening and closure are used to time PS and ES points and ES or dicrotic notch pressure (P) is estimated using Weber's equations (ES P=0.4 systolic BP + 0.6 diastolic BP). LV dimension (LVD), posterior wall thickness (PWT) and P at PS and ES are used to determine mid-wall LV meridional wall stress (WS): $WS=0.334\ P(LVD/(PWT(1+PWT/LVD)))$. PS WS in 13 normals (173 $\pm$32x 10^3 dynes/cm) was similar to published values obtained invasively. In 4 subjects with LV decompensation PS overlapped normal (227 + 116) but ES WS ((144 + 53) greatly exceeded normal (42 $\pm$ 10, $p<0.01$). As expected, in 14 compensated hypertensives PS WS (144 + 53) and ES WS (44 +21) did not differ from normal. Plots of PS and ES WS vs. LVD clearly differentiated normal, depressed and "unloaded" LV function. With this method, load alteration with nitrates, leg raising or tourniquets can be used to generate ES FL lines which reflect intrinsic LV contractility and reveal the consequences of therapeutic load reduction. We conclude that noninvasive FL analysis is a valuable new technique for assessment of LV performance.

SENSITIVITY AND SPECIFICITY OF THE PULMONIC VALVE ECHOGRAM IN THE DETECTION OF PULMONARY HYPERTENSION

Roy Kaku, MD; Alexander Neumann, BS; William Bommer, MD; Lynn Weinert, BS; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis, Calif.

Little data are available regarding the sensitivity and specificity of the pulmonic valve echogram in the detection of pulmonary hypertension (PHT). Thus simultaneous pulmonic echograms were evaluated in 52 patients with normal pulmonary artery pressure and 46 patients with PHT (mean pressure >20 mm Hg). Maximum A wave depth (Amax) bore a general correlation with pulmonary pressure ($r = .70$) and was >2 mm in all normals (mean 3.4). Amax was less in PHT (1.1 $p<.01$) and was absent in 7 of 27 PHT patients with sinus rhythm. A mid-systolic notch was recorded in 15 of 22 PHT patients, but no normals, in whom pulmonic echograms were recorded throughout systole. The ratio of right ventricular pre-ejection period to ejection time (PEP/RVET) correlated with pulmonary artery pressure ($r = .70$) and was greater than 6.3 in all but 2 PHT patients (mean .43). PEP/RVET was less in normals (.26, $p<.001$) and was greater than 0.3 in only 3. The opening velocity (OV) of the pulmonic echogram did not correlate with pulmonary artery pressure nor was OV different in normals as compared to PHT: (369 vs 363 mm/sec). Diastolic slope (EF) of the pulmonic echogram also did not correlate with pulmonary pressure, but EF was less in PHT than normals: 34 vs 26 mm/sec ($p<.05$). Thus, considerable overlap exists in all measurements of the pulmonic echogram between normals and patients with pulmonary hypertension. However, no normals exhibited an Amax <2 mm if in normal sinus rhythm or a mid-systolic notch, and thereby these criteria may be utilized to indicate the presence of pulmonary hypertension.

ECHOCARDIOGRAPHIC DETERMINATION OF MITRAL VALVE FLOW IN NORMAL SUBJECTS AND IN PATIENTS WITH CORONARY ARTERY DISEASE, CARDIOMYOPATHY OR MITRAL REGURGITATION

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The purpose of this study was to derive and test a clinically applicable method for calculating flow across the mitral valve(MV). Based on data derived from MV echograms which were manually traced on a digital tabloid and entered into a graphic terminal for computer analysis, a formula was derived for calculating MV stroke volume (SV-MV) using mitral EE(vertical distance between leaflets in mm at the E point) and DE slope(mm/sec), electrocardiographic PR interval(sec), and heart rate (HR).

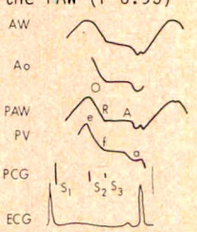
$$SV\text{-}MV = \left(\frac{EE}{HF} + PR\right) \times 100 + \frac{2 \times DE}{HR}$$

This formula was tested prospectively on 80 consecutive patients from whom 95 simultaneous MV echograms and either thermodilution(TD) [45] or Fick(FI) cardiac outputs (CO) [50] were performed. Of the 80 patients, 16 were normal; 54 had coronary artery disease; 3 had cardiomyopathy;and 7 had nonrheumatic mitral regurgitation(MR). For the 73 patients without MR, there was no statistical difference in SV-MV vs SV-TD or SV-FI nor in CO-MV vs CO-TD or CO-FI when data were compared using either the Student t test; Mann-Whitney U test; or the Kolmogorov-Smirnov test.SV-TD ranged from 24-83 cc (mean 56 cc) and SV-FI ranged from 35-139 cc (mean 78 cc). Linear regression(r) for stroke volume was .90 ± 6 cc and for cardiac output was .83 ± .5 liter. The presence or absence of ventricular asynergy did not alter statistical findings. For the 7 patients with MR, SV-MV consistently overestimated forward stroke volume. This study shows that, for these 80 patients, the MV echogram reflects mitral valve flow.

PHYSIOLOGIC CORRELATES OF PULMONARY VALVE MOTION IN DIASTOLE

David J. Pocoski, MD; Pravin M. Shah, MD, FACC; Linda Sylvester, University of Rochester Medical Center, Rochester, NY

The diastolic pulmonary valve (PV) waveform has been correlated with pulmonary hypertension. This study examined the relationship and further correlated it with changes in left atrial (LA) size as reflected by the posterior aortic wall (PAW) motion. Complete diastolic PV waveforms were obtained in 55 patients. The e-f slope of the PV correlated with the O-R slope of the PAW ($r=0.95$) and the interval S2-f correlated with the S2-R ($r=0.94$) and neither parameter correlated with pulmonary arterial pressure (PAP). In all patients with mitral stenosis both the PV e-f and the PAW O-R slopes were flattened irrespective of PAP. In patients with a normal left atrial index (≤2.0 cm/M^2) stroke volume index (SVI) correlated with e-f slope ($r=0.60$) and the slope was flattened in all patients with significantly reduced SVI. The e-f slope was uniformly flat with a large LA. PAP was normal in 72% of patients with pulmonary valve "a dips" > 2 mm and was elevated in 75% of patients with absent "a dips" reflecting the instantaneous pressure differences across the PV in diastole. The numerous exceptions suggested other factors. The A wave PAW correlated with the "a dip" PV ($r=0.85$). Conclusion: The early diastolic waveform of the PV, like the PAW, reflects underlying LA events due to anatomical proximity. The e-f slope is not a measure of PAP. The "a dip" is a complex event related to PAP and other factors which include LA events.



ASSESSMENT OF MITRAL VALVE E POINT-SEPTAL SEPARATION AS AN INDEX OF LEFT VENTRICULAR FUNCTION IN ACUTE AND CHRONIC ISCHEMIC HEART DISEASE

Wilbur Lew, MD; Hartmut Henning, MD; Heinz Schelbert, MD; Joel Karliner, MD, FACC, University of California, San Diego

We compared a new echo index of left ventricular (LV) function, mitral valve E point-septal separation (EPSS), to the radionuclide ejection fraction (EF) calculated from the first pass method in 60 patients (pts) (73 studies) with ischemic heart disease. Thirty-eight pts had acute myocardial infarction (MI) and 22 pts were studied an average of 24 months after acute MI. In 30 normals EPSS ranged from 0 to 5.4 mm (average = 1.3 mm). In 57 studies (78%) EPSS correctly identified pts with a normal or reduced EF (< 0.52), but in 13 studies (18%) EPSS was normal and EF depressed. In only 3 studies (4%) was there a normal EF and an abnormal EPSS. Results did not differ between pts with acute MI and those studied late after MI. An EPSS of >5.5 mm was highly specific (89%) for a reduced EF, but sensitivity was only 65%. Abnormal wall motion by echo and/or videotracking occurred equally among pts with normal and increased EPSS, but EPSS was less accurate in pts with more severe wall motion abnormalities. EPSS was unrelated to heart rate; an abnormal EPSS was equally distributed among pts with a normal vs an enlarged echo LV end-diastolic dimension. EPSS was superior to other echo indices of LV function (% of fractional shortening, mean Vcf and EF). Thus, EPSS is a simple noninvasive measure of LV function. We conclude that an abnormal EPSS is useful for identifying depressed LV function in patients with acute MI and chronic ischemic heart disease; however, a normal EPSS can be associated with normal as well as reduced LV performance and therefore is not of value in the assessment of LV function in such patients.

NON-INVASIVE ASSESSMENT OF LEFT VENTRICULAR FUNCTION FROM PEAK MITRAL CLOSING VELOCITY BY M-MODE ECHOCARDIOGRAPHY. Bodh Jugdutt, MBChB, Simon Lee, MD, FACC, University of Alberta, Canada.

Final mitral valve (MV) closure and ejection of blood into the aorta are mediated by left ventricular (LV) contraction. The rate of MV closure should therefore be a reflection of LV contractile function. The relation of peak MV closing velocity (ds/dt), from the echogram of the anterior MV leaflet (ECHO), to peak aortic ejection velocity (V) and acceleration (dV/dt), and to the peak first derivative of LV pressure rise (dp/dt) was studied in 18 open chest dogs. ECHO, aortic velocity by flow probes and high fidelity LV pressure were recorded on magnetic tape under resting conditions and after interventions to change dp/dt and V. The signals were differentiated electronically and the various parameters analyzed on a beat-to-beat basis. Average resting ds/dt was 26.9±9.0 (SD) cm/sec, and changed significantly ($p < .001$) after isoprenaline (39.7±15.0), propranolol (20.9±10) and coronary occlusion (11.3±3.6). These changes in ds/dt followed directional changes in V, dV/dt and dp/dt and correlated significantly ($p < .001$) with V ($r = .82$), dV/dt ($r = .67$) and dp/dt ($r = .73$). Aortic cross-clamping decreased ds/dt ($p < .001$).

In man, ECHO was recorded during routine cardiac catheterization. Aortic flow and LV pressure were measured by transducer tipped catheters in 10 patients. Resting ds/dt was 25.5±1.6 cm/sec in 6 normals, and separated 24 coronary patients with resting end-diastolic pressure (EDP) < 14 mmHg from 12 with EDP > 14mmHg (26.0±8.3 vs 16.9±4.2 cm/sec. The ds/dt correlated with dp/dt ($r = .93$, $p < .01$) and V ($r = .81$, $p < .005$), and angiographic ejection fractions ($p < 0.01$).

Thus, ds/dt from ECHO provides a useful tool for the objective, non-invasive assessment of LV function in man.

A REVIEW OF 40 PATIENTS WITH ATRIAL MYXOMA SEEN OVER A 20-YEAR PERIOD. Lise-Andrée Mercier, MD, FRCP(C); Martin G. St. John Sutton, MB, MRCP; J. T. Lie, MD, FACC; Emilio R. Giuliani, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Forty patients (pts) with atrial myxoma confirmed at surgery or autopsy in the last 20 years were analyzed to determine the efficacy of cardiac catheterization and echocardiography in diagnosis and the long-term follow-up. They were divided into 2 groups: 19 pts seen in 1957-67 (Group I) and 21 pts seen in 1968-77 (Group II). Definitive diagnosis was made preoperatively in 8 of 19 pts (42%) of Group I and 19 of 21 pts (90%) of Group II ($P < 0.001$). Before 1968 (Group I), diagnosis was missed in 11 pts (58%) and confirmed by catheterization in 7 of 19 (37%) and chest x-ray in 1 of 19 (5%). There was one death after angiography in this group. Since the introduction of echocardiography in 1968 (Group II), only 2 pts were undiagnosed preoperatively (10%); diagnosis was confirmed by echocardiography in 12 of 21 (57%), catheterization in 6 of 21 (29%), and chest x-ray in 1 of 21 (5%) without any major complication. Overall (Groups I and II), false-negative diagnoses were made in 25% by catheterization and in 7% by echocardiography. Time from onset of symptoms to death or surgery was the same (16.8 mo) in both groups. The incidence of embolization, heart failure, or syncope was similar (31%, 45%, 19% in Group I and 33%, 59%, 12% in Group II, respectively). Preoperative mortality was 16% (3 of 19) in Group I and 0% in Group II. Overall operative mortality was 2.5%. There were 3 late deaths (2 unrelated to myxoma) and 1 recurrence over a mean follow-up of 7.8 yr. We submit that in pts with atrial myxoma, echocardiography is replacing catheterization as the major diagnostic technique because of its safety, reproducibility, and reliability. Long-term postoperative results in these patients have been excellent.

CIRCUMFERENTIAL SEGMENTAL WALL MOTION OF THE LEFT VENTRICLE ESTIMATED FROM PHASED-ARRAY SECTOR SCAN ULTRASOUND IMAGES
John D. Hestenes, Ph.D., Ming K. Heng, M.D., H.L. Wyatt, Ph.D., Samuel Meerbaum, Ph.D., Eliot Corday, M.D., FACC, Robert Nathan, Ph.D., Jet Propulsion Laboratory, Calif. Institute of Technology, Pasadena, California.

The study of circumferential motions of the myocardium on a regional basis requires landmarks that can be tracked. Strong local ultrasound echoes at the surface and interior of the myocardium have relative positions that change with cardiac contraction. Mapping distances between points provides parameters that correlate with segmental wall motion. Time sequences demonstrate changes in magnitude and direction of vectors between echoes consistent with cardiodynamics before and after occlusion of the left anterior descending (LAD) artery. Ultrasound phased array (Varian V3000, 2.25 MHz) sector images from closed-chest dog studies were digitized and processed at JPL. Feature extraction (512 x 512 pixels) after appropriate image enhancement included epicardial and endocardial boundaries, their enclosed areas and the area centroid points. In 6 trials on one image the standard deviations for an 15.23 cm^2 area was 0.53 cm^2, 0.5 mm for centroid coordinates and 0.2 mm or less for the center-of-mass of strong echoes and about 3% for optical density. At the papillary muscle level circumferential shortening in segments of the septum, anterior papillary muscle and between papillary muscles was 86%, 70%, and 80% in normals. This method appears to be sensitive to changes that occur between pre- and post-occlusion conditions. The non-invasive aspect of these measurements permit a new approach to studies of ischemic heart disease and the therapeutic regimens for salvage of jeopardized myocardium.

DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY: AN ECHOCARDIOGRAPHIC STUDY OF 81 PATIENTS WITH AUTOPSY CORRELATION IN 25 SUBJECTS
Ravi Prakash, MD, FACC, Hossein Alimadadian, MD, Paul Lindsay, MD, University of California, Irvine, Ca.

Electrocardiograms (ECG) and echocardiographic (Echo) measurements of right ventricular wall thickness (RVWT) were obtained in 81 patients to evaluate right ventricular hypertrophy (RVH). Twenty-five of 81 subjects also had necropsy studies. Correlations between the Echo and necropsy RVWT were found to be good in all 25 subjects studied at necropsy ($r = 0.82$), including 9 with RVH (necropsy RVWT $\geq$ 5 mm; $r = 0.88$), and 16 without RVH (necropsy RVWT $\leq$ 4 mm; $r = 0.82$). The diagnosis of RVH by ECG correlated poorly with necropsy and Echo findings. Based on the necropsy criteria of RVH, 43 of 81 patients (53%) had RVH (Echo RVWT $\geq$ 5 mm;) 8 of these 43 patients had ECG evidence of RVH (81% false negative). Based on the necropsy criteria of RVH, 38 patients were without RVH (Echo RVWT $\leq$ 4 mm); 7 of these 38 patients had ECG evidence of RVH (18% false positive). Diagnosis of RVH was difficult by ECG in 45 patients with RBBB, LBBB, LVH, and/or old myocardial infarction; however, the Echo measurements of RVWT were useful in diagnosing RVH in these patients. We conclude that Echo measurements of RVWT are more reliable than the ECG in diagnosing RVH. Echo may be particularly useful in diagnosing RVH in the presence of conduction defects, myocardial infarction, and/or bi ventricular hypertrophy where ECG diagnosis is especially difficult.

THURSDAY, MARCH 9, 1978
PM
CARDIOVASCULAR HEMODYNAMICS
1:45 to 4:00

THE HEMODYNAMICS OF PULSUS PARADOXUS IN PERICARDIAL TAMPONADE
Gregory S. Uhl, MD, Barry R. Alter, MD, Joseph P. Murgo, MD, FACC; John R. Logsdon, MD; Harold G. Felter, MD; George M. McGranahan, Jr., MD, FACC, Brooke Army Medical Center, Fort Sam Houston, Texas

The mechanism of pulsus paradoxus (PP) in pericardial tamponade (TAMP) was studied during pericardiocentesis in two patients. Simultaneous intrapericardial pressures (IPP), pulmonary wedge (PWP), electromagnetically derived aortic and pulmonary flow velocities and right (R) and left (L) heart hi-fidelity pressures were obtained using multisensor catheters. Six normal subjects served as controls. R and L stroke volumes (SV) were derived from flow velocity recordings. Pressure and flow data were analyzed over multiple respiratory cycles. In the controls, during inspiration (INSP), right stroke volume (RSV) increased 12% above the mean, while left stroke volume (LSV) decreased 10%. In expiration the reverse situation occurred, with an 8% decrease in RSV and an equal increase in LSV. In TAMP, this normal variation is exaggerated. During INSP, RSV increased 60% with a similar decrease in LSV. In expiration, RSV decreased 33%, with a comparable increase in LSV. This would suggest that during INSP, as R ventricular filling occurs, the interventricular septum encroaches upon the L heart, decreasing its potential end-diastolic volume, and resulting in a decreased SV. During expiration, as R ventricular volume decreases, the L ventricle is allowed to fill completely as reflected in its increased SV. Thus, PP in TAMP appears predominantly to be a result of competition by the R and L ventricles for a fixed intrapericardial space. In addition, PWP dropped below IPP in TAMP (-3 mmHg) during INSP allowing for potential pulmonary venous pooling. This mechanism may also contribute to decreased filling of the L ventricle.

THE DEMONSTRATION OF SEGMENTAL PERFUSION DEFECTS IN HYPERTROPHIC CARDIOMYOPATHY IMITATING CORONARY ARTERY DISEASE
Victor F. Huckell, MD, Howard M. Staniloff, MD, David H. Feiglin, MD, Garry W. MacKenzie, MD, Robert W. Wald, MD, E. Douglas Wigle, MD, John E. Morch, MD; Peter R. McLaughlin, MD, FACC, Toronto General Hospital, Toronto, Canada.

Myocardial perfusion was studied with Thallium-201 (Tl-201) in 18 patients (pts) with hypertrophic cardiomyopathy, mean age 40 years. Although all pts had a history of pain on exercise, maximal exercise ECG's were not diagnostic of ischemia. Selective coronary arteriograms were performed in 10 pts-9 normal and 1 isolated 75% left anterior descending obstruction. Outflow tract obstruction was absent in 3, latent in 4 and present at rest in 11 (3 mild, 8 severe). All studies were analyzed by 3 independent observers. Multiple perfusion defects were seen in the pt with left anterior descending obstruction. Of the 13 pts with both rest and exercise studies, there were 4 pts with fixed perfusion defects, 7 with new perfusion defects on exercise and 2 normal studies. Of the 5 pts with only exercise studies, 3 were normal while 2 had perfusion defects. There was no relation between severity of gradients and the size or location of the segmental perfusion defects. Segmental perfusion defects may be seen in hypertrophic cardiomyopathy in the absence of coronary artery disease suggesting cellular loss, cellular dysfunction or regional malperfusion. New exercise perfusion defects despite normal coronary arteries suggest ischemia as a mechanism for chest pain.

CHRONIC, SEVERE PULMONARY HYPERTENSION: THE EFFECT ON RIGHT VENTRICULAR FUNCTION WITH AND WITHOUT DIGITALIZATION
C.B.Mullins,M.D.,F.A.C.C., J.L.Harper, J.E.Jones, D.L. Burleson, University of Texas Health Science Center at Dallas, Dallas, Texas.

Chronic pulmonary hypertension results in progressive right ventricular dilatation, hypertrophy and tricuspid regurgitation. Potentially digitalis could decrease the rate of dilatation, hypertrophy and the magnitude of tricuspid regurgitation. Pulmonary artery banding was used to elevate the mean pulmonary artery pressure to 40 mmHg (100/15 mmHg phasic) in 16 closed chest dogs and maintained for 6 months, eight were digitalized (digoxin serum levels 1.2 Ng/ml). Biplane cineangiographic right ventricular (RV) volumes and pressures were obtained at control and every 30 days for 6 months. Progressive changes were noted monthly in both groups. Comparing preband studies with studies at 180 days in both groups; tricuspid regurgitation resulted in 12% of the stroke volume (SV) in the digitalized group (D) and 14% of the SV in the nondigitalized control group (C); SV decreased 11% in C and 17% in D; end systolic volume increased 111% in D and 107% in C; end diastolic volume increased 35% in D and 24% in C; ejection fraction decreased 37% in D and 32% in C; dpdt increased 61% in D and 38% in C; cardiac output decreased 13% in D and 20% in C. Pathological studies showed a two-fold increase in RV free wall weight and thickness (hypertrophy) in both groups. These findings indicate that rapid and progressive changes in right ventricular function occur as a result of severe pulmonary hypertenion and digitalization does not significantly alter the course of these changes.

DYNAMIC GEOMETRY OF LEFT ATRIUM AND LEFT VENTRICLE IN ACUTE MITRAL REGURGITATION
Shigetake Sasayama,MD; Masaaki Takahashi,MD; Genta Osakada,MD; Hiroya Hamajima,MD; Kunihiko Hirose,MD; Eizo Nishimura; Chuichi Kawai ,MD; Univ. of Kyoto, Kyoto,JAPAN

Instantaneous transverse diameter(D) of left atrium(LA), left ventricular(LV) circumferential segment length(SEG) and anterior papillary muscle length along its long axis (APM) were measured throughout cardiac cycle using miniature ultrasonic dimension gauges together with LA and LV pressure(P) in 11 open chested dogs. In control, LAD decreased from 19.6±1.5 to 18.5±1.4 mm with LA contraction. During LV ejection, percent shortening was 25% in SEG and 10% in APM, while LAD increased continuously to 20.3±1.6 mm with concomitant rise in LAP. Following Mitral valve opening, LAD and LAP decreased rapidly. The graded mitral regurgitation(MR) was then produced by cutting chordae tendineae one after another. With moderate MR, end-diastolic(ED) length(L) of SEG increased by 24%($p<.01$) with extent of shortening(ΔL) being augmented by 96%($p<.01$). EDL of APM increased by 7%($p<.01$) with 60% augmentation of ΔL($p<.01$). LAP was sharply elevated with prominent a and v waves. LA(ED)D was enlarged to 22.8±2.2 mm ($p<.01$) associated with increased LA shortening (1.0±.2 to 1.9±.4 mm $p<.01$) and LA expansion during LV systole (1.8±.3 to 3.3±.5 mm $p<.01$). As MR was increased by additional chordal rapture, EDL and ΔL continued to increase both in SEG and APM. LAP was elevated higher (a wave was 23 mm Hg, v wave was 43 mm Hg). LA(ED)D further increased to 24.6±2.5 mm($p<.01$). However, the amplitude of LA shortening and expansion decreased (1.2±.4 and 1.9±.8 mm respectively). In severe MR, nitroprusside and isoproterenol decreased LAP and LAD restoring active LA contraction. Thus, acute onset of MR enhanced booster function of LA initially but conduit function took place in later severe MR. Response of APM was substantially less than in SEG.

AREA SHRINKAGE FRACTION OF MYOCARDIAL WALL: A NEW MODEL FOR ASSESSING SEGMENTAL ASYNERGY

Geun C. Jang, MD; George T. Daughters II, MS; Neil B. Ingels Jr., PhD; Edwin L. Alderman, MD, FACC, Cardiology Division, Stanford University Medical Center and Palo Alto Medical Research Foundation, Palo Alto, CA.

Left ventricular (LV) ejection results from shrinkage of myocardial wall area. Seven patients (pts) who had mid-wall tantalum markers implanted at the time of coronary surgery, were studied by computer-aided fluoroscopy in control and post-nitroglycerin (NTG) states to evaluate the applicability of Area Shrinkage Fraction (ASF). ASF is defined as the ratio of segmental myocardial wall areas at end-diastole and end-systole, computed from 8 convex areas of truncated hemicones of the LV as shown in the figure. Mean (m) ejection fraction (EF) was 51% (range 35-73%) and m total ASF was 28% (range 18-35%). Of 56 segments in 7 pts (8 per LV) 14 segments (24%) were unchanged, 23 (39%) increased and 21 (37%) decreased in segmental ASF (ASF_S) in post-NTG states. Nine (16%) of 56 segments had ASF_S <10%. Of 5 pts who had negative ASF_S, indicating dyskinesis, 4 pts improved and one decreased in ASF_S post-NTG intake. All pts had both increase and decrease in ASF_S in one or more segments post-NTG, including 3 pts who had normal EF. This method quantitates segmental asynergy and demonstrates sensitivity in detecting segmental asynergy in both control and drug intervention states. We propose that this 3-dimensional model can better quantitate segmental asynergy by using truncated cone geometry of LV than can other methods based on linear dimensions, and could be applied to contrast or 2-dimensional echoventriculography for clinical use.

EFFECT OF FILMING PROJECTION AND INTEROBSERVER VARIABILITY ON ANGIOGRAPHIC LV VOLUME DETERMINATION.

William J. Rogers, M.D. FACC, L. Richard Smith, William P. Hood, Jr., M.D. FACC, John A. Mantle, M.D. FACC, Charles E. Rackley, M.D. FACC and Richard O. Russell, Jr., M.D. FACC, University of Alabama Medical Center, Birmingham, Alabama.

Although biplane RAO/LAO quantitative left ventricular (LV) angiography is commonly performed, justification for LV volume calculation using the area-length method (originally formulated from AP/LAT angiograms) has not been provided. To assess whether RAO/LAO and AP/LAT LV volumes are similar when computed by the same area-length method formulae, we performed biplane cine LV angiography in both RAO/LAO and AP/LAT projections in random sequence in 21 patients and in 4 plaster casts of known volume. LV silhouettes were drawn independently by 2 trained observers. Calculated angiographic volume (AV) of the plaster casts correlated almost exactly with true volume (TV) (r=0.999, AV=.98 TV + 1.2), establishing the absolute accuracy of this system. Excellent agreement between end-diastolic volume (EDV) (ml) and end-systolic volume (ESV) (ml) was found between the 2 observers (EDV: 191 ± 46 (mean ± SD) vs 188 ± 46, r=0.98; ESV: 99 ± 47 vs 97 ± 48, r=0.99 and EF: 0.50 ± .12 vs 0.50 ± .12, r=0.94). Furthermore there was excellent agreement between the 2 filming projections (AP/LAT vs RAO/LAO) (EDV: 190 ± 49 vs 189 ± 45, r=0.90, ESV: 98 ± 49 vs 98 ± 46, r=0.97 and EF: 0.50 ± .12 vs 0.50 ± .13, r=0.91). The variation between methods was not significantly different from the variation between observers.

The data thus demonstrate excellent interobserver agreement in quantitative biplane LV angiography and suggest that filming projection (RAO/LAO vs AP/LAT) does not significantly influence LV volumes calculated by the area-length method. Use of the area-length method in calculating RAO/LAO biplane LV volumes is therefore justified.

REPRODUCIBILITY OF VENTRICULAR FUNCTION MEASUREMENTS BY ANGIOGRAPHIC AND RADIONUCLIDE ANGIOGRAPHY

Gene B. Trobaugh, MD; J. Ward Kennedy, MD, FACC; Glen W. Hamilton, MD; James L. Ritchie, MD, FACC; Harborview Medical Center and Seattle Veterans Hospital, Seattle, Wa.

Forty-two consecutive single plane (30° RAO) contrast ventriculograms were performed utilizing a GE Fluoricon 300 angiographic system. End diastolic volume (EDV) and end systolic volume (ESV) were calculated by the area-length method by three experienced observers. Ten other consecutive patients had 2 Tc-99m in vitro tagged red cell radionuclide determinations of ejection fraction performed 30 minutes apart; the results were analyzed by two experienced observers. Equilibrium studies were accumulated utilizing a high speed, r wave synchronized, computer reconstruction. Images were recorded in the anterior and 45° LAO position by an Ohio Nuclear series 100 gamma camera with high sensitivity collimation.

Reproducibility of angiographic EDV: r ranged from .89 to .94. In the total of 126 differences, 80% were < 25cc. Reproducibility of angiographic ESV: r ranged from .93 to .95; 82% of differences were < 15cc. Selection of films judged good-excellent improved reproducibility of the ESV: r=.99. The mean difference was < 15cc in 91% of the 69 pairs. For films judged poor by at least one of the three observers, the difference was < 15cc in 75% (n=57 pairs) (p=.005). Reproducibility of angiographic ejection fraction (A-EF): r ranged from .87 to .90; for the total of 126 differences, 63% were < .05; 87% were < .10.

Reproducibility of radionuclide-EF: r=.99, which is significantly more than A-EF: for the 20 differences, 85% were < 0.05 and 98% were < 0.10; p=.008 and .006, respectively. Reproducibility of repeated studies: r=.995.

This study documents the reproducibility of angiographic measurements; radionuclide determinations of EF are more reproducible than angiographic EF determinations.

ESTIMATION OF LEFT VENTRICULAR VOLUMES IN MAN FROM BIPLANE OBLIQUE CINEANGIOGRAPHY

Joshua Wynne, MD; Laurence H. Green, MD; Tift Mann, MD; David Levin, MD; William Grossman, MD, FACC, Peter Bent Brigham Hospital, Boston, Massachusetts

Evaluation of left ventricular geometry and contractile performance has traditionally been assessed by biplane left ventriculography in the anteroposterior and lateral projections. In patients with coronary artery disease, it has been suggested that right and left anterior oblique (RAO/LAO) views of the left ventricle (LV) may permit more optimal evaluation of regional wall motion. However, the validity and accuracy of LV volumes calculated from RAO/LAO projections has not been demonstrated. Accordingly, 11 casts prepared from human postmortem left ventricles were cined in the 30° RAO/LAO position, and volumes were calculated (V_C) using the area-length method. True volume (V_T) was assessed by volume displacement and ranged from 15-185 cc. V_C always exceeded V_T, but with close correlation (r) and small standard error of the estimate (SEE): V_T=0.98 V_C-8.9 cc, r=0.99, SEE=8 cc. The slight overestimation resulted in part from foreshortening of the long axis (L) of the LV in the LAO position: (L_{RAO} 8.5 ± 0.3 cm vs L_{LAO} 6.4 ± 0.2 cm, $p < 0.01$). In a single case, biplane volumes calculated in several degrees of RAO/LAO obliquity (0-40°) were compared. There was a 23% variation in L_{LAO} and a 25% variation in V_C. In addition to the obliquity of position, L_{LAO} was altered by the degree of forward tilt of the apex.

CONCLUSION: Ventricular volumes can be measured accurately from biplane RAO/LAO cineangiography using the area-length method. However, strict standardization of the degree of obliquity is necessary to offset the variation of L_{LAO} that occurs due to ventricular foreshortening.

TOE TEMPERATURE AS A PROGNOSTIC INDICATOR OF CIRCULATORY SHOCK

Robert Henning, MD; Sergio Valdes, MD; Fred Wiener, Ph.D.; Marcia Thompson, RN; Max Harry Weil, MD, FACC, University of Southern California, Los Angeles, California

Peripheral skin perfusion may be objectively assessed in patients in circulatory shock by the measurement of the gradient between toe and ambient temperatures (T-A). Thermistor probes were applied to the ventral surface of the first toe of each foot and were inserted into the rectum for a distance of at least 8 cm. Thermistor probes were also mounted at the bedside for ambient temperature monitoring. Toe, rectal, and ambient temperatures were measured at 15 min. intervals in 68 patients in shock due to myocardial infarction (32), blood culture proven bacteremia (21), and hypovolemia (15) with measured blood volume reduced to <70% of normal. Changes in T-A were compared to changes in intraarterial pressure, cardiac index, and arterial blood lactate. In 36 survivors, T-A increased 5.2C but only 1.3C in 32 fatalities ($p < .001$). T-A proved to be a better discriminator between survivors and fatal cases in cardiogenic shock than blood lactate, cardiac index, or arterial pressure. In bacterial shock, T-A was comparable to arterial blood lactate in assessing the severity and likelihood of survival and significantly better than measurement of cardiac index and arterial pressure. In the instances of hypovolemic shock, T-A was comparable to measurements of arterial pressure and better than the measurement of cardiac output in distinguishing between survivors and fatal cases. When T-A was consistently 2C or less, the outcome was fatal. The T-A temperature gradient provides an inexpensive, a uniquely simple, non-invasive, and quantitative indicator of the severity of cardiogenic shock.

PROGNOSTIC VALUE OF POSITIVE Tc99m PYROPHOSPHATE SCINTIGRAMS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Masood Ahmad, M.D.; K. William Logan, Ph.D.; Richard H. Martin, M.D., FACC. VA Hospital and University Medical Center, Columbia, Missouri.

We followed 30 patients (pts), age range 52-75 years, with acute myocardial infarction (MI) and positive Tc99m Pyrophosphate (Tc99m-PYP) myocardial scintigrams for a mean time of 25 months. None of the patients had previous MI and all survived the initial hospitalization. We examined the long term prognostic significance of the positive scintigrams. Development of angina, congestive failure, ventricular arrhythmias and recurrent MI were listed as complications. The intensity of uptake in all scintigrams with 3+ to 4+. Based on the extent and pattern of uptake following types of scintigrams were identified. Type A: uptake localized to one area; Type B: extensive uptake involving more than one area; Type C: doughnut pattern uptake; Type D: diffuse uptake. Data in various patient groups based on the type of scintigram are tabulated below:

Scintigram	# of pts	% Complications	% Mortality
Type A	11	45	0
" B	5	60	20
" C	6	100	83
" D	8	12	0

The high mortality rate in patients with a Type C scintigram as compared to patients with Types A and D was significant ($p<0.001$ Fisher's exact test). These data indicate a poor long term prognosis for patients with acute myocardial infarction and a doughnut shaped Tc99m-PYP uptake.

THURSDAY, MARCH 9, 1978
PM
CLINICAL APPLICATION OF CARDIAC ISOTOPES
1:45 to 4:00

TOMOGRAPHIC MYOCARDIAL IMAGING WITH POSITRON EMITTING AGENTS

Harischandra Karunaratne, MD; Paul Harper, MD; Sema Cantez, MD; Leon Resnekov, MD, FACC; Frank Atkins University of Chicago, Chicago, Illinois.

We have utilized the potential tomographic characteristics of detecting positron decay annihilation photons in coincidence by an imaging device consisting of two opposed uncollimated gamma cameras, to obtain myocardial tomograms and compare them with conventional gamma camera images in the same patient. In 5 patients with healing infarcts and 2 normal volunteers 300,000 count immediate consecutive tomographic images were compared with ^{201}Tl images, containing the same number of counts. In 6 further patients with healing infarcts, $^{13}NH_4^+$ myocardial tomograms were compared with conventional gamma camera $^{13}NH_4^+$ images using tungsten collimation. Unprocessed ^{81}Rb myocardial tomograms were not superior to ^{201}Tl images in detecting and delineating uptake defects. In 3 of the 6 patients with healing infarcts studied with $^{13}NH_4^+$, uptake defects not seen in the conventional gamma camera images were visualized in the tomographic images. These additional defects were seen even in unprocessed back projection tomograms. With computer processing to remove out-of-focus data, the delineation and contrast of the tomographic images were markedly improved. Such processing also has the potential of quantitating the extent of myocardial uptake defects. It is concluded that positron emission tomography of the heart--a) even when unprocessed, gives myocardial images of at least comparable quality to conventional gamma scintigrams, and b) when processed, provides greatly improved contrast and delineation of uptake defects.

PROGNOSTIC IMPLICATIONS OF A PERSISTENTLY POSITIVE TECHNETIUM-99m-PYROPHOSPHATE MYOCARDIAL SCINTIGRAM AFTER ACUTE MYOCARDIAL INFARCTION

Harold Olson, M.D.; Kenneth Lyons, M.D.; Wilbert Aronow, M.D., F.A.C.C.; Joan Orlando, M.D.; John Kuperus, M.S.; and David Hughes, M.D.; University of California, Irvine

To assess the independent prognostic value of technetium-99m-pyrophosphate myocardial scintigraphy (PYPS) after acute myocardial infarction (AMI), 109 clinically stable ambulatory patients (pts) had a PYPS 6-288 weeks (31.1 ± 43.3 weeks) after AMI. Of the 109 pts, 61 (56%) had a positive PYPS (localized pattern 30 pts, diffuse pattern 31 pts). At follow-up 4-89 weeks (49.8 ± 21.1 weeks) after their PYPS, 11 of 109 pts (10%) had a cardiac death, and 7 of the 109 pts (6%) had a nonfatal AMI. Ten of 61 pts (16%) with a positive PYPS had cardiac death compared to 1 of 48 pts (2%) with a negative PYPS ($P<0.02$). Six of 61 pts (10%) with a positive PYPS had a nonfatal AMI compared to 1 of 48 pts (2%) with a negative PYPS (P not significant). Of 61 pts with a positive PYPS, 16 (26%) had either cardiac death or nonfatal AMI compared to 2 of 48 pts (4%) with a negative PYPS ($P<0.01$). At follow-up, 34 of the 98 surviving pts (35%) had either compensated congestive heart failure (CHF) or Functional Class III angina. Twenty-six of 51 pts (51%) with a positive PYPS had CHF or Functional Class III angina compared to 8 of 47 pts (17%) with a negative PYPS ($P<0.001$). We conclude from our follow-up data that pts with a persistently positive PYPS following AMI have an increased incidence of severe angina, CHF, nonfatal AMI, and cardiac death.

MITRAL VALVE PROLAPSE - EVIDENCE FOR A MYOCARDIAL PERFUSION ABNORMALITY

Donald D. Tresch, FACC, Jagmeet S. Soin, Ronald Siegel, Michael Love, Michael H. Keelan, Jr., Medical College of Wisconsin, Milwaukee, Wisconsin

Fifteen patients (pts.), 11 females and 4 males, ages 14-50 years, with ECHO documented MVP had combined treadmill stress test (ST) and myocardial perfusion imaging (MPI). At peak exercise 1mCi of Tl-201 was injected IV and multiple view MPI was performed 20 minutes later using a gamma camera. Ten of 15 (66%) had abnormal MPI involving the apical-diaphragmatic or lateral regions. Stress EKGs were positive in 4 of the 10 pts. with abnormal MPI. Contrast studies in 6 of these 10 pts. revealed normal coronary arteries with mild to moderate mitral regurgitation secondary to MVP.

Clinical manifestations (arrhythmias and chest pain) were more significant in the pts. with abnormal MPI, and resting EKG abnormalities (T-wave inversion) were found only in pts. (6/10) with perfusion defects.

In conclusion, a high incidence (66%) of stress myocardial perfusion abnormalities are demonstrated in pts. with MVP and normal coronary arteries. This study supports the hypothesis that decreased regional myocardial blood flow or abnormal cellular function occurs in MVP, and may offer an explanation for the clinical manifestations of this abnormality.

DIAGNOSTIC VALUES OF DUAL MYOCARDIAL IMAGING FOR ACUTE MYOCARDIAL INFARCTION.

Young Il Kim, MD, FACC; Ralph J. Gorten, MD; John F. Williams, Jr., MD, FACC; Akira Nishimura, MD. The University of Texas Medical Branch, Galveston, TX

To diagnose acute myocardial infarction (AMI), 135 patients (pts) with suspected AMI underwent myocardial imaging with both Tc-99m pyrophosphate (PYP) and Thallium-201 (Tl) obtained 2.9 and 3.7 days (means) respectively after onset of symptoms. Of these pts, 63 had both images on the same day. By clinical criteria, of 103 pts without old infarction (Group A), 62 had AMI and 41 no AMI, and of 32 pts with old infarction (Group B), 14 had new AMI and 18 no AMI. In Group A; sensitivity and specificity of PYP (94% and 81%) and Tl (95% and 85%) were similar and when combined, all pts with AMI had abnormal image(s) with one or both tracers (sensitivity = 100%) and only one pt without AMI had both images abnormal. Excluding 19 with discordant images, 84/103 (82%) pts had both images concomitantly abnormal or normal with the corresponding predictive value of 98% for AMI and 100% for no AMI in this subset. In Group B; both images were concomitantly abnormal in 12/14 (86%) pts with AMI as well as in 6/18 (33%) pts without AMI whereas only one pt with AMI had both images normal. Thus, combined tracers yielded a screening value for AMI exceeding the individual tracers, will serve as an independent definitive diagnostic method in a subset of pts without prior infarction, but require additional diagnostic aids in pts with discordant images or prior infarction.

TECHNETIUM-99m HEPARIN; A NEW RADIOPHARMACEUTICAL TO IDENTIFY DAMAGED CORONARY ARTERIES AND DAMAGED MYOCARDIUM

Padmakar Kulkarni, PhD; Robert Parkey, MD; L. Maximilian Buja, MD, FACC; James Wilson, MD; Frederick Bonte, MD; James Willerson, MD, FACC, University of Texas Health Science Center, Dallas, Tx.

Preliminary experimental results suggested that technetium-99-m heparin (TcH) may be useful for identifying experimentally damaged coronary arteries. Both temporary coronary artery occlusion (T) and permanent occlusion (P) coronary models were designed to exam TcH as a possible means to localize and scintigraphically identify damaged coronary endothelium (DCE) or myocardium (DM). Of 16 dogs, 4 had P of the proximal left anterior descending coronary artery (LAD); 12 had T of the LAD for 60-85 min followed by reflow. Three-six mCi of TcH was injected IV within 5-10 min post-release in the T and 48 hrs post-occlusion in the P dogs. Scintigrams and blood samples were obtained serially for up to 3½ hrs and the dogs were sacrificed for histology and well counting. Of the 12 T dogs, 9 had transmural damage; 1 had subendocardial damage only; 2 had no obvious damage at all. The 9 with transmural damage showed increased uptake of TcH in the damaged tissue [ratios % injected dose to normal left ventricle (R)]. R were border epicardium (BEP) 1.52 (1.14-2.10); border endocardium (BE) 1.79 (1.12-2.60); damaged epicardium (DEP) 10.1 (2.04-27.4); damaged endocardium (DE) 15.5 (6.97-36.5). Four P dogs showed BEP 1.77 (1.29-2.04); BE 2.01 (1.54-2.90); DEP 3.45 (2.93-3.70); DE 4.50 (3.44-6.01). In 4 T dogs the LAD was divided into 3 parts. R above the site of occlusion was 3.45 (2.88-4.24); at site of occlusion was 12.8 (9.82-14.1); below the site of occlusion 5.14 (4.01-5.75); R in circumflex artery was 2.49 (2.04-3.04). Scintigrams were positive in vivo in T dogs; the P dogs were visualized only in vitro. Results suggest TcH may have value as a positive imaging agent when coronary arteries or myocardium is injured and reflow into the damaged area is provided.

USEFULNESS AND LIMITATIONS OF THALLIUM-201 FOR DETECTION OF CORONARY ARTERY DISEASE BASED ON BAYES THEOREM

Gene B. Trobaugh, MD; Glen W. Hamilton, MD; James L. Ritchie, MD, FACC; David Williams, PhD; Harborview Medical Center and Veterans Administration Hospital, Seattle, Wa.

Thallium-201 (TL) rest-exercise (R-Ex) imaging was performed in 137 patients. Significant coronary artery disease (CAD) was present in 107 and absent in 30 by arteriography. Sensitivity (SENS) and specificity (SPEC) for CAD was 52% and 83% for Ex ECG ST depression (ST↓); 66% and 85% for ECG Q wave and ST↓; 66% and 97% for Ex TL; 77% and 93% for R-Ex TL; and 90% and 80% for combined R-Ex TL ECG. The probability (p) of CAD for a normal (N) or abnormal (ABN) result was calculated for R-Ex ECG and TL alone or combined at CAD prevalences (PREV) from 1-99%.

R-Ex TL was superior to ECG (Q or ST↓) for detecting CAD at all PREV of CAD and provided greater discrimination (DIS) between pCAD with an ABN test and pCAD with a N test. The DIS is maximum for Ex ST↓ at a pre-test pCAD = .40 where the pCAD with an ABN test is 65% and 30% with a N result. The DIS is greatest at pre-test pCAD <.50 with Ex TL; discrimination is maximum at pre-test pCAD =.25, where the pCAD with an ABN test is 90% and 10% with a N result. The DIS and the pCAD with an ABN result both fall rapidly below a pre-test pCAD of .10. The DIS is greatest at pre-test pCAD >.50 with combined R-Ex TL + ECG; discrimination is maximum at pre-test pCAD =.60, where the pCAD with an ABN test is 90% and 15% with a N result. If the pre-test pCAD =.80, the pCAD with an ABN result is 95%, and 35% with a N test. At higher pre-test pCAD, the pCAD with a N test increases rapidly.

These results indicate that (1) screening with TL in asymptomatic populations is probably unwarranted and (2) the most appropriate use of TL in the evaluation of possible CAD is in those whose pCAD is judged clinically to be 20-60%.

SPECIFICITY OF THALLIUM 201 MYOCARDIAL IMAGING IN PATIENTS WITH CHEST PAIN AND SUSPECTED CORONARY ARTERY DISEASE. Malcolm Pond, MD; Terry Rehn, MD; Ian Bailey, MD; Bertram Pitt, MD, FACC; and Lewis Becker, MD, FACC. Johns Hopkins University, Baltimore, Maryland.

Thallium 201 myocardial perfusion imaging after exercise (Ex-MPI) has been used increasingly to diagnose coronary artery disease (CAD) in patients (pts) with chest pain syndromes. Although the incidence of false positive Ex-MPI is low in normal young volunteers, the specificity of Ex-MPI has not been fully evaluated in pts with chest pain who are found to have minimal or no CAD by angiography. We studied 53 pts (age range 23 to 65) with < 50% stenoses using rest and Ex-MPI. Seven pts had mitral valve prolapse, 10 had suspected coronary artery spasm, and 36 had no demonstrable heart disease. Thirty-seven had normal left ventricular function on angiography, while 12 had regional wall motion abnormalities and 4 had generalized ventricular dysfunction. Rest electrocardiograms (ECG) showed nonspecific ST segment abnormalities in 24 pts. Rest and Ex-MPI were performed in 3-4 views and graded as normal, equivocal, or abnormal by at least two observors blinded to pt identity and diagnosis. Ex-MPI showed defects in 5 pts. Specificity of Ex-MPI was therefore 48/53 (91%). Positive Ex-MPI did not relate to abnormal ventricular function, mitral valve prolapse, or suspected coronary spasm. Twelve pts had false positive exercise ECG; of these, only one had false positive Ex-MPI. Rest MPI were graded as equivocal in 13 and abnormal in an additional 4; 8 of these pts "normalized" after Ex-MPI.

Thus, Ex-MPI is highly specific for CAD. Rest MPI may be misleading in pts with chest pain syndromes not associated with CAD, since abnormal or equivocal areas are frequently seen.

THURSDAY, MARCH 9, 1978
PM
ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY—IV
1:45 to 4:00

THE EFFECTS OF DIGITALIS ON REFRACTORINESS AND REENTRY WITHIN THE HIS PURKINJE SYSTEM IN MAN
Joseph A. Gomes, MD, FACC; Malkiat S. Dhatt, MD, FACC; Masood Akhtar, MD, FACC; Anthony N. Damato, MD, Cardiology Dept., USPHS Hospital, Staten Island, New York

Digitalis (D) prolongs refractoriness (ref) of the atrioventricular node (AVN) precluding assessment of the drug's effect on the His Purkinje system (HPS). Using His bundle electrograms and the ventricular extrastimulus method, effects of D on retrograde (Ret) ref of the HPS, AVN and on interventricular reentry (Re) within the HPS were studied in 16 patients (pts). Ouabain .01 mg/kg was given IV and studies repeated after 30 minutes. Following D there was a significant decrease in the effective refractory period (ERP) of the ventricular muscle (VM) (244±34 to 233±24 msec $p<.005$) (±SD) but no significant change in the functional refractory period (FRP) (472±52 to 477±62 msec NS) or the ERP of the HPS (300±21 to 298±19 msec NS). Of 13/16 pts with intact VA conduction, in 5/13 pts with slow VA conduction (relative to antegrade), D increased Ret ERP and FRP of AVN. In contrast, in 8/13 pts with faster VA conduction, D had no effect on Ret ref of AVN. The phenomenon of Re-HPS characterized by a reentrant beat (V_3) at critical Ret conduction delays in the HPS (V2 H2) within a narrow range of V_1 V_2 intervals was seen in 9/16 pts. D increased and shifted to the left the zone of Re in 7/9 pts (46±23 to 65±23 msec, $p<.001$) and decreased it (10-30 msec) in 2 pts. The critical V_2 H_2 (189±28 to 195±28 msec NS) and V_1 V_2 for Re (301±21 to 299±34 msec NS) did not significantly change, but the longest V_2 H_2 (for any V_1 V_2) increased after D (226±40 to 238±37 msec $p<.025$). Conclusions: D (1) significantly decreases ERP of VM (2) has no appreciable effect on Ret ref of the HPS (3) widens the zone of Re-HPS due to shortening of the ERP of VM with attainment of longer V_2 H_2 delays and (4) has different effects on slow and fast Ret AVN conduction.

COMBINED THALLIUM-201 MYOCARDIAL IMAGING AND MULTIPLE GATED BLOOD POOL STUDIES IN CHILDREN
David L. Gilday, M.D., F.R.C.P. (C); Robert Howman-Giles, M.D.; Richard Rowe, M.D., F.R.C.P. (C); The Hospital for Sick Children, Toronto, Ontario

Myocardial perfusion and muscle mass are now easily determined in children using Thallium 201 (TL201) citrate (1.15 mCi/m2). The ability to non-invasively determine focal ischemic areas of myocardium in children who present with heart failure and no overt signs of congenital heart disease has been a major advance in pediatric cardiology. When followed by a multiple gated study in the LAO and anterior projections the information gained by non-invasive means is valuable.

We have studied 33 children over 1 year of age. The primary problem was to determine if a focal ischemic area of myocardium was present. Nine children with myocardopathies all had marked thinning of the left ventricular free wall and chamber enlargement. Five had very poor contraction with ejection fractions less than .25. The other 4 had reasonable contraction visually but reduced ejection fraction ranging from .4 to .5. It was easy to separate these from children with thickened muscular hypertrophy in IHSS (2) or pulmonary hypertension (2).

Four children with focal ischemic disease were easily detected, one of whom had cardiac dilatation and poor contraction.

The combination of these 2 non-invasive procedures has resulted in improved diagnosis, prognostic ability and especially follow up after treatment, as these studies are easily performed as out-patients.

VERAPAMIL THERAPY IN PATIENTS WITH SUPRAVENTRICULAR TACHYARRHYTHMIA
Paul J. Troup, MD; Douglas P. Zipes, MD, FACC, Krannert Institute of Cardiology, Indiana University School of Medicine, Veterans Administration Hospital, Indianapolis, Indiana.

The purpose of this study was to evaluate the effects of verapamil (V), a slow channel blocker, in 6 patients (pts) (52 yrs mean, 4M,2F) with symptomatic paroxysmal supraventricular tachycardia (PSVT), atrial flutter (AFl) or atrial fibrillation (AF). V was infused IV over 60 sec at a low dose (LD, .075 mg/kg) followed by a high dose (HD, 0.15 mg/kg) 30 min later if LD was ineffective. In 3 pts with PSVT (2 with WPW) lasting 0.25 to 9 hrs, 2 episodes were converted to sinus rhythm (SR) 125 sec (mean) after infusion of LD and 1 episode was converted to SR 135 sec after infusion of HD. Mean ventricular rates decreased from 190 to 93/min. Failure to restore SR occurred in 1 pt with concealed WPW in whom PSVT slowed from 180 to 162/min. In 2 pts with AFl, lasting 1 1/2 and 12 hrs, V LD was followed by AF and slowing of the mean ventricular rate from 170 to 95/min within 90 sec (mean). SR returned 1 1/2 and 9 1/2 hrs later. In 1 pt with AF lasting 1 1/2 hrs, V LD was followed by intermittent SR in 25 sec and slowing of the ventricular rate from 180 to 120/min. Sustained SR occurred 55 min later. One pt with PSVT was receiving aprindine, and all pts with AFl or AF were receiving digoxin (0.85 ng/ml, mean serum concentration) at the time of V infusion. Mean blood pressure 2 min after ineffective V response decreased from 121/96 to 114/87 mmHg, and after effective V response from 104/69 to 103/69 mmHg. No pt experienced undesirable reaction from V. We conclude that V given IV is an excellent drug for acute treatment of PSVT, AFl or AF.

DIFFERING EFFECTS OF ATRIAL AND VENTRICULAR BIGEMINY ON MYOCARDIAL EXCITABILITY AND CONDUCTION. Boaz Avitall, PhD, Stephen G. Pauker, MD, FACC, Herbert J. Levine, MD, FACC, and Shapur Naimi, MD, FACC. Tufts-New England Medical Center, Boston, Massachusetts.

Atrial or ventricular bigeminy was produced in 6 paced dogs by stimuli delivered to atrium(A) or ventricle(V). Premature beats(PB) were adjusted to produce coupling intervals of 400, 350, 300 and 250 ms. Strength-interval curves, defining the recovery of excitability following APBs and VPBs, were determined by delivering computer controlled anodal stimuli of increasing intensity to the ventricle at varying intervals after the premature beat until a propagated response was evoked and its conduction time measured. Decreasing the coupling interval of VPBs caused shortening of the refractory periods (108±6 to 87±14 ms, P<.001) and prolongation of conduction times (120±19 to 127±25 ms), favoring re-entrant arrhythmias. This was not observed with APBs. Moreover, for APBs anodal dip thresholds, corresponding to the vulnerable period, rose (591±151 to 686±166 μa, P<.05) when coupling intervals were decreased. In contrast, for VPBs anodal dip thresholds tended to fall (463±224 to 391±257 μa) when coupling intervals were decreased. There were no significant changes in late diastolic thresholds.

Thus, closely coupled VPBs increased ventricular vulnerability to arrhythmias by an adverse effect on parameters favoring re-entry, suggesting a possible mechanism for the R-on-T phenomenon. Conversely, APBs with comparable coupling intervals had no such adverse effect. Finally, the data suggest that the relatively benign nature of APBs compared to VPBs may not be entirely due to the protective effect of the atrio-ventricular node but may, in part, reflect their differing effects on the excitability and conduction of the ventricular myocardium.

TRICYCLIC ANTIDEPRESSANT OVERDOSE: PLASMA LEVELS AND ELECTROCARDIOGRAPHIC FINDINGS

Rene A. Langou, MD; Craig Van Dyke, MD; Peter Jatlow, MD; David Bailey, MD, Yale University School of Medicine, New Haven, Ct.

Plasma levels (PL) of amitriptyline (A) or imipramine (I) and their respective pharmacologically active N-desmethyl metabolites (nortriptyline, desmethylimipramine) were measured in 30 patients (pts) with overdose (OD), (6 male and 24 female). Age ranged from 13 to 73 yrs. All but 7 pts had previous psychiatric histories and none had cardiovascular disorders.

The tricyclic PL ranged up to 1260 ng/ml for A and to 1732 ng/ml for I. Tachycardia occurred in 70% (21/30) of pts; hypotension in 33% (10/30); and cardiac arrest in 10% (3/30). In 21 pts in whom complete ECG data were recorded; prolonged QT interval occurred in 90% (19/21); widened QRS in 33% (7/21), abnormal ST-T waves in 33% (7/21), prolonged PR interval in 19% (4/21) and normal ECG in 10% (2/21). ECG findings did not correlate with PL. However pts with widened QRS had significantly higher PL than those without it. The ratios of parent drug level to that of the metabolite (P/M) were much higher ($\geq$ 2) than those of pts on chronic therapy and were diagnostic of pre-steady state, characteristic of acute OD.

Plasma tricyclic levels are of limited clinical value in OD, but a P/M $\geq$ 2.0 suggests acute OD. Tachycardia, prolongation of the QT interval, and widened QRS complex, are common ECG manifestations of tricyclic OD. These electrocardiographic findings are extremely helpful in the diagnosis of OD.

THE ATRIAL ELECTROGRAMS OF COARSE ATRIAL FIBRILLATION AND FLUTTER-FIBRILLATION

Stephen F. Schaal, MD, FACC; Carl V. Leier, MD, Ohio State University, Columbus, Ohio

Intracardiac atrial electrograms were analyzed in 44 patients (pts) during coarse atrial fibrillation (CAF) and/or flutter-fibrillation (FF) in order to determine the patterns of atrial electrical activity. Right atrial (RA) electrograms were recorded from the high and low right atrium and left atrial (LA) electrograms were recorded from the coronary sinus and/or from an esophageal bipolar catheter. A variety of atrial electrical activity was demonstrated during CAF and FF. Thirty-five pts showed typical biatrial fibrillation with intermittent regularity. Thirty-three pts demonstrated periods of dissimilar atrial rhythms with RA flutter and LA fibrillation in 15, RA fibrillation and LA flutter in 11, flutter or fibrillation of one atrium and quiescence of the other atrium in 4, flutter of one atrium and atrial tachycardia of the other in 2, and independent flutter of each atrium in 1. Dissimilar rhythms occurred within the RA in 5 pts with flutter of one part of the atrium and fibrillation in the remaining portion. Fragmented flutter (atrial electrogram deflection > 80 msec in duration with fragmentation) presented as CAF and FF on the scalar ECG of 6 pts. Eleven pts had fast flutter (AA interval < 180 msec) of both atria during the scalar ECG recording of CAF and/or FF. This study shows that during the scalar ECG recordings of CAF and FF the atria may demonstrate a wide spectrum of electrical activity including biatrial fibrillation with periods of regularity, dissimilar inter- and intra-atrial rhythms of several different varieties, fragmented flutter and fast flutter.

THE SIGNIFICANCE OF AUTONOMIC BLOCKADE IN THE EVALUATION OF SINUS NODE DYSFUNCTION. B. Massie, MD; J. O'Young, BS; M. Scheinman, MD, FACC; H. Strauss, MD, FACC; R. Peters, MD; J. Desai, MD; San Francisco General Hospital, San Francisco, California.

The results of electrophysiologic testing in patients (PTS) with sinus node dysfunction (SND) often correlate poorly with symptom severity and ECG abnormalities. This discrepancy has been ascribed to changes in autonomic tone during study and to the heterogeneity of pathologic processes underlying SND. To better delineate the pathophysiology of SND we subjected 11 PTS with clinical and ECG evidence of SND (3 with sinus pauses or exit block, 5 with bradycardia-tachycardia and 3 with chronic bradycardia) to combined blockade by propranolol (.15 mg/kg I.V.) and atropine (.04 mg/kg I.V.). The post-blockade (B) intrinsic heart rate (IHR) was compared to previously published normal values of this parameter (IHR=120.3-.58xage±8.1[SD]). IHR was >2SD below normal in 6 PTS (Gp I) including 2 from each ECG subgroup, and was normal in 5 PTS (Gp II). Control (C) sinoatrial conduction time (SACT) and C and B sinus node recovery times (SNRT) and 2nd-10th post-pacing cycle lengths (PPCL) were measured.

	Gp I: C	B	Gp II: C	B
†SACT	4/6		0/5	
†SNRT	2/6	4/6	0/5	0/5
†PPCL	3/6	4/6	1/5	2/5

Gp I PTS had significantly (p<.001) more C abnormalities and developed additional positive tests after B, suggesting removal of compensatory autonomic effects. Only 1 Gp II PT had a positive C test, which was abolished by B. Two other Gp II PTS displayed infrequent prolonged PPCL only after B. Our results indicate that a subset of PTS, identifiable by slow IHR, had more severe SND affecting both automaticity and conduction. Furthermore, autonomic influences may obscure some abnormalities and produce others.

HIS BUNDLE BLOCK: A PROSPECTIVE EVALUATION

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The clinical course of patients (pts) with His bundle block (HBB) is uncertain though this group is considered to be at increased risk of bradyarrhythmias. We've identified 38 pts with HBB, 18 with a split His (SH) (mean age 52 years) and 20 with a prolonged HV and a narrow QRS (mean age 60 years). Of those with SH, 14 had associated bifascicular disease. The interval between His potentials was 28msec (range 9 to 75). SH was brought out only by pacing in 7. Eleven had dizziness (D) or syncope (S). Four received pacemakers (PM); one died suddenly 2 weeks later. All 14 pts without PM are alive at an average of 12 months after His bundle study; 2 have had recurrent S of uncertain cause.

Fifteen out of 20 pts with prolonged HV and narrow QRS presented with D or S. Seven pts had sick sinus syndrome and 5 had Mobitz II A-V block. The mean HV interval was 76.2msec (range 57 - 180). With pacing, block below H was produced in 5 pts. Thirteen pts received PM, one of whom has died; another has had S. All 7 without PM are alive after a mean followup of 26.1 months.

HBB is usually accompanied by other conduction abnormalities. PM are indicated for symptomatic bradyarrhythmias. Our policy of not using prophylactic PM in HBB pts without documented bradyarrhythmias has not resulted in deaths due to heart block.

QRS AXIS DEVIATION IN APACHE CHILDREN

Gordon A. Ewy, M.D., F.A.C.C., Robert D. Okada, M.D., Frank I. Marcus, M.D., Stanley J. Goldberg, M.D., Marian N. Molthan, M.D., Brendan P. Phibbs, M.D., F.A.C.C., University of Arizona, Tucson, Arizona.

We have previously reported a tenfold increase in the incidence of left axis deviation (LAD) and a twofold increase in the incidence of right axis deviation (RAD) in Navajo children compared with recorded incidences in general populations of children. This study was undertaken to see if this finding was unique to this tribe. Resting electrocardiograms were obtained from 144 Mescalero Apache Indian children between ages 12 and 14 with negative cardiac history and normal physical examination. LAD (-1° to -90°) was found in 17 children, or 12%. Of these, the axis was between -30° to -44° in 3 children, or 2%, and between -45° to -90° in 3 children, or 2%. RAD (+91° to +180°) was found in 27 children, or 19%. Extreme axis deviation (+181° to +269°) occurred in two children, or 1%. None had left anterior hemiblock, left bundle branch block, or right bundle branch block. This study demonstrates an eightfold increase in the incidence of LAD and a twofold increase in the incidence of RAD in Apache children when compared to reported incidences in general populations of children. The present study supports our previous conclusion that there is a hereditary basis or predisposition to the development of axis deviation. Hereditary axis deviation must be considered as a cause of frontal plane QRS axis from -1° to -90° and from +91° to +180°.

VECTORCARDIOGRAPHIC CORRELATIONS IN LEFT VENTRICULAR ASYNERGY DUE TO CORONARY ARTERY DISEASE. II. INFERIOR SEGMENT

Eliot Young, MD; Gerald H. Angoff, MD; R. Barrett Steelman, MD, FACC; Harold D. Levine, MD, FACC; Peter F. Cohn, MD, FACC, Peter Bent Brigham Hospital, Boston, MA.

A previous study from our laboratory in patients with coronary artery disease (CAD) has demonstrated the value of the vectorcardiogram (VCG) in estimating severity of anterior and apical asynergy. The purpose of the present study was to determine the value of the VCG in estimating severe asynergy of the inferior segment. The inferior segment was defined as the middle portion of the entire inferior surface (measured from the aortic valve to the tip of the apex) of the left ventriculogram in the right anterior oblique view. The inferior segment was analyzed in 270 consecutive patients with angiographically proven CAD. In 40 of the 270, the inferior segment showed akinesis or marked hypokinesis. Hemiaxial shortening was $\leq$ 10% in 36 of the 40, and the other 4 had 11-15% shortening. In 35 of the 40, the frontal plane QRS loop showed a markedly abnormal inferior infarct pattern: early superior forces $\geq$ 0.028 sec and the ratio of the leftward deviation of these early forces to the inferior deviation of the loop $\geq$ 0.9. These findings were not seen in the other 230 patients with less severe or no asynergy. The results indicate a new use for the VCG in estimating asynergy of the inferior segment, and also suggest that it may be helpful in quantitating the extent of an inferior infarct, a measurement known to be difficult to estimate from the electrocardiogram.

THURSDAY, MARCH 9, 1978
PM
SPECIAL TOPICS IN CARDIOLOGY
1:45 to 4:00

PROGNOSTIC FEATURES OF IDIOPATHIC CONGESTIVE CARDIOMYOPATHY

Joseph McClellan, MD; Bruce Waller, MD; Jack Segal, MD, FACC; John Stapleton, MD; W. Proctor Harvey, MD, FACC, Georgetown University Medical Center, Washington, DC

Over 600 patients with cardiomyopathy were evaluated in a study unit since 1958. 123 patients who had idiopathic congestive cardiomyopathy by strict clinical criteria or autopsy were analyzed. The initial functional class, physical findings, chest X-ray and EKG's were evaluated and followed at least 5 (and up to 19) years or until death. Patients were usually identified because of CHF, arrhythmias, emboli or other symptoms. 77 patients died (48 autopsied) with an average survival of 6.2 years. The causes of death were CHF 48%, sudden 29%, arrhythmia 10%, emboli 3%, other 10%. The most important predictors of survival were initial heart size (2.1 years average survival in patients with moderately severe to severe cardiomegaly vs. 7.7 years in patients with minimal to moderate cardiomegaly) and functional class (average survival with initial Class I was 8.6 years; Class II, 5.6 years; Class III, 3.9 years; Class IV, 3.4 years). No patient had an improvement in heart size or functional class prior to death. Patients with atrial fibrillation, an episode of ventricular tachycardia (VT), or multifocal PVC's had a decreased average survival (3.2 years, 3.4 years, and 4.8 years respectively). The presence of LAD, LBBB, or unifocal PVC's were not correlated with reduced survival. Sudden death occured in 29% of the patients but could not be correlated with heart size, the presence of atrial fibrillation, unifocal PVC's, LAD, LBBB or prior embolic episodes. There was a higher incidence of sudden death in patients with a prior episode of VT (64%).

THE SPECTRUM OF CARDIAC SARCOIDOSIS:A CLINICOPATHOLOGIC STUDY OF 83 PATIENTS.

Kenneth J. Silverman, M.D., Grover M. Hutchins, M.D., Bernadine H. Bulkley, M.D., F.A.C.C. The Johns Hopkins Medical Institutions, Baltimore, Md.

Although sarcoid may involve the myocardium, there is little information on its true incidence or significance. To examine this we studied 83 consecutive autopsied patients with sarcoidosis. The patients ranged in age from 18 to 80 years (average 46) and 60% were women; 22 (27%) of them had myocardial granulomas: in 9 (41%) these were clinically silent, and in 13 (59%) there was a history of heart failure and/or arrhythmias and conduction defects. Of the 22 patients only 4 (18%) had grossly evident, widespread myocardial lesions: 3 of these 4 (75%) had documented ventricular arrhythmias. All 4 had sudden unexpected death at an average age of 36 and in only 2 had sarcoid been suspected during life. The other 18 patients (82%) had trivial myocardial involvement with lesions evident only microscopically. Of these, only 2 (11%) had ventricular arrhythmias, 7 (39%) conduction block and 4 (22%) sudden death.

Comparing the 22 patients with and the 61 without cardiac sarcoid, those with cardiac lesions had 4 times (x) more ventricular arrhythmias, 3 x more heart block, and 2 x more sudden death. Sudden death was as common, however, in patients without cardiac sarcoid as in those with only histologically evident lesions. Congestive heart failure was as frequent in patients with and without cardiac sarcoid, and correlated more with systemic hypertension.

The results show that although myocardial involvement occurs in over 25% of patients with sarcoid, it is most often morphologically trivial and clinically silent. Arrhythmias and heart block are more common inthe cardiac sarcoid group, but the findings suggest that only that small subset of patients with severe grossly evident myocardial sarcoid are at increased risk for sudden death.

MALIGNANCY FOLLOWING CARDIAC TRANSPLANTATION

Jeffrey L. Anderson, MD; John G. Krikorian, MD; Charles P. Bieber, MD; Edward B. Stinson, MD, FACC, Divisions of Cardiology and Oncology, and Cardiovascular Surgery Dept., Stanford Medical Center, Stanford CA.

Experience with de novo malignancy complicating organ transplantation has previously accumulated for series of renal but not cardiac transplant recipients. From January, 1968, to April, 1977, 124 patients had undergone cardiac transplantation at Stanford. All were followed to August, 1977, or until death (mean and median follow-up of 18.3 and 9.7 months, respectively), and none were lost to follow-up. Seven malignancies occurred, 4.5 to 61.9 months after surgery. Malignancy was responsible for 4 (11%) of the 35 deaths occurring later than 3 months following surgery. Lymphoproliferative disease occurred in the 3 youngest of the 7 patients: one (26 yrs) died of extensive unclassified visceral lymphoma; one (19 yrs) died of diffuse histocytic lymphoma (DHL) involving lung and cerebellum; and one (14 yrs) has entered prolonged remission following radiotherapy for primary DHL of brain. A 45 yr old patient receiving cyclophosphamide developed fatal acute myelogenous leukemia. Adenocarcinoma of colon, metastatic to liver, led to the death of a 54 yr old patient. Two long-term survivors developed squamous cell carcinomas of skin. A high frequency of HLA antigens A1 and B8 occurred in the malignancy group. Mean age in the 7 patients was less, but not significantly so. Number of rejection episodes, type of immunosuppressive agent, blood type, underlying disease, and sex did not differentiate those developing malignancy. Cardiac and renal transplantation appear to involve a similar risk of de novo malignancy consequent to long-term immunosuppression. The risks of malignancy warrant consideration, especially in younger patients being evaluated for cardiac transplantation. An aggressive approach to primary DHL of brain is indicated.

ANGIOGRAPHIC APPEARANCE OF CORONARY ARTERIES IN CONSTRICTIVE PERICARDITIS

Jonathan Alexander, MD; Steven Wolfson, MD, FACC; Michael J. Kelley, MD, FACC; Lawrence S. Cohen, MD, FACC; Rene A. Langou, MD, Yale University School of Medicine, New Haven, Connecticut

The motion of the coronary arteries (CA) during angiography was assessed in patients (pts) with 1) constrictive pericarditis (CP), 2) cardiomyopathy (CM), and 3) normals (NM). CP was established in 7 pts by characteristic right and left heart hemodynamics and surgical pathology. Four had calcific CP and 3 had non-calcific CP. All underwent left ventriculography (LVgram) and coronary arteriography. All had normal ejection fractions (EF), >55%. The 10 CM pts had abnormal EF (mean 25 ±3 SEM) and normal CA. The 10 NM pts had normal hemodynamics, LVgram and CA.

A normal pattern of systolic foreshortening (SF) of the coronary artery branches (distal and proximal segments moving toward each other) was observed in all NM pts. Normal SF was noted in 9/10 CM pts. Absent SF, in the one CM patient occurred in association with akinesis of the corresponding left ventricular segment on LVgram. Six/seven CP pts had coronary arterial segments with no SF, despite normal LVgrams and EF. The CP patient with normal SF did not have demonstrable pericardial calcification.

Thus, absent SF of the CA with normal LVgram is suggestive of CP and is probably due to entrapment of the epicardial CA within the fibrotic pericardium. This angiographic sign may suggest the diagnosis in unsuspected CP.

THE MYTH OF REDUCED AORTIC AND LEFT ATRIAL SIZE IN ATRIAL SEPTAL DEFECT

Leslie E. Oliver, MD; Dean T. Mason, MD, FACC; Hugo Bogren, MD, FACC; Lily George, MD; and Anthony N. DeMaria, MD, FACC, University of California, Davis, California.

Although it is widely held that aortic and left atrial size are diminished in patients with atrial septal defect (ASD), few data are available to support this contention. Therefore aortic and left heart chamber dimensions in 24 patients with catheter documented ASD were compared to 20 normals (N) by echocardiography, cineangiography and qualitative estimation of aortic size by chest x-ray. Stroke index was similar in ASD and N: (mean) 37.5 vs 42.8 ml/M^2 by dye-dilution and 35.1 vs 36.3 ml/M^2 by angiography (both NS); as was shortening fraction by echo: .34 vs .36 (NS). Echographic left ventricular diastolic dimension index was less in ASD than N: 2.5± vs 3.0 cm/M^2 ($p<.02$); however diastolic volume index by angio was similar in these groups: 50.1 vs 52.9 (NS). Importantly, the size of the aorta was similar in ASD and N 1.7 vs 1.7 cm/M^2 by echogram and 1.6 vs 1.5 cm/M^2 by angiogram (both NS), while both left atrial and left atrial to aortic ratio were greater in ASD than N: 2.2 vs 1.9 (NS) and 1.3 vs 1.1 cm/M^2 respectively ($p<.02$). Although aortic size was estimated to be small in 12 of 24 (50%) ASD patients by chest x-ray, no differences existed in aortic measurements by echocardiography or angiography from patients judged to have normal sized aortas. Thus, these data do not support the long held belief that stroke volume is reduced and aortic and left atrial size are diminished in patients with atrial septal defect.

FURTHER EXPERIENCES IN CLINICAL USE OF A NEW FLEXIBLE ENDOMYOCARDIAL BIOPSY CATHETER FOR THE LEFT VENTRICLE

Chuichi Kawai, MD; Shigetake Sasayama, MD; Akira Matsumori, MD, The Third Division, Department of Internal Medicine, Kyoto University, Kyoto, Japan.

Design and method of practical use of a new endomyocardial biopsy catheter specifically made for the left ventricle will be presented using 35mm slides and 16mm cine films. Since the left ventricle is the chamber mainly involved in many adult patients with cardiomyopathy, biopsy specimens from the left ventricle are generally more informative than those from the right in search for structural changes in cardiomyopathy. The Konno-Sakakibara biopsy catheter has proved practical and safe, at least for right ventricular biopsy. However, because of its stiffness, the Konno-Sakakibara biopsy catheter is sometimes difficult to pass through the aortic valve into the left ventricle via the retrograde transaortic approach. The new flexible biopsy catheter consists of ordinary intracardiac catheter with an operating handle at one end and cutting pincers at the exploring end. By rotating a knob on the operating handle, the tip of the biopsy catheter can be bent approximately 40 degrees in one plane. The biopsy catheter measures 120cm in length and 3.0 to 3.5mm in diameter. With this instrument the left ventricle was successfully entered in 100 per cent in retrograde fashion through the femoral artery in 10 patients with cardiomyopathy, and nearly 25 specimens were obtained. The specimens were subjected to light and electron microscopic examinations, catecholamine staining and immunofluorescent studies. Untoward complications have never been encountered. It is concluded that left ventricular biopsy will be performed more easily and safely with this new flexible biopsy catheter.

THE DIFFERENTIATION OF MILD AORTIC STENOSIS FROM AN INNOCENT PULMONIC EJECTION MURMUR

W.G. Guntheroth, MD., J.G. Stevenson, MD., I. Kawabori, MD and T.K. Dooley; University of Washington, Seattle

A common-and difficult-problem is a grade 2-3 basal ejection murmur in an asymptomatic child, with normal ECG and xray. If the conclusion is mild aortic stenosis, prophylaxis against SBE is required, and there is a risk of progression to early calcific aortic stenosis. We have compared our clinical conclusions to the results of pulsed Doppler-echocardiography (PDE) in 40 consecutive children referred for this differential diagnosis. Our clinical diagnosis of aortic stenosis was based on an ejection murmur that was prominent at the 2nd right interspace(but not necessarily louder than at the pulmonic area), which transmitted well to the neck; additional criteria were the presence of an ejection click and an early diastolic whiff. PDE criteria included aortic leaflet eccentricity, abnormal turbulence in the ascending aorta or at the level of the aortic valve, and aortic insufficiency. Clinically we diagnosed aortic stenosis in 30 of the 40 patients. PDE confirmed abnormal turbulence at the aortic valve in 26, and in the ascending aorta in 24. Leaflet eccentricity was present in 20, and insufficiency in 12. In the 4 subjects without aortic PDE abnormalities, 1 had PDE-evidence of pulmonary insufficiency, 1 had abnormal systolic turbulence in the pulmonary artery, and 2 had no detectable abnormalities by PDE. In the 10 youngsters clinically diagnosed as having an innocent murmur, 3 had abnormal turbulence at the aortic valve and ascending aorta, and 1 of those had valve eccentricity. We conclude that our clinical criteria are reasonably specific (87%) but less sensitive (70%). Pulsed Doppler-echocardiography is a powerful non-invasive assistance for this important differential diagnosis.

HEPATIC FAILURE IN ALCOHOLIC CARDIOMYOPATHY PATIENTS

Eric C. Rackow, M.D., Kings County Hospital, S.U.N.Y. Downstate Medical Center, Brooklyn, New York

It is generally stated that patients with alcoholic cardiomyopathy rarely have hepatic failure. Therefore, a review of all patients with alcoholic cardiomyopathy who underwent postmortem examination at KCH from 1965 to 1970 was conducted in order to determine the incidence of hepatic failure and effect of auto-anticoagulation. The criteria for the diagnosis of alcoholic cardiomyopathy were 1: chronic abuse of alcohol, 2: no evidence of the usual causes of heart disease, and 3: postmortem diagnosis of cardiomyopathy. The criteria for the diagnosis of hepatic failure were 1: prolongation of the prothrombin time more than 3 seconds over control, and 2: postmortem diagnosis of Laennec's cirrhosis. Twenty-five patients fulfilled the criteria for the diagnosis of alcohlic cardiomyopathy. None of these patients were medicated with anticoagulants. Twelve of the 25 patients (48%) had hepatic failure (HF), and 13 patients had no hepatic failure (NHF). The prothrombin time was increased to 20.5/12.5 (±2.1/0.5 SD) seconds in HF patients compared to 12.9/12.1 (±0.6/0.3 SD) seconds in NHF patients ($P < 0.01$). None of the 12 (0%) HF patients had mural thrombi at postmortem examination, whereas 6 of 13 (46%) NHF patients had both left and right sided mural thrombi ($P < 0.01$). The incidence of pulmonary emboli at postmortem examination was 2 of 12 (17%) in HF patients and 9 of 13 (69%) in NHF patients ($P < 0.05$). In conclusion, hepatic failure is common in patients with alcoholic cardiomyopathy, and the auto-anticoagulation appears to protect them from the development of mural thrombosis and pulmonary thromboembolism.

ABSENCE OF PARADOXICAL PULSE IN PATIENTS WITH ATRIAL SEPTAL DEFECT AND CARDIAC TAMPONADE

Itzhak Kronzon, MD; Howard E. Winer, MD, New York University Medical Center, New York, N.Y.

Four patients with atrial septal defect (ASD) and cardiac tamponade (CT) were studied by echocardiography. The diagnosis of ASD was established by catheterization in 3 and at post mortem in 1. CT was caused by infection in 2 patients and by tumor in the remaining 2. All had high central venous pressures, cardiomegaly and severe hypotension. None had paradoxical pulse (PP). Each echocardiogram showed a large pericardial effusion and manifestations of ASD, including dilatation of the right ventricle and paradoxical motion of the interventricular septum. The previously described echocardiographic signs of CT (inspiratory decrease in left ventricular internal dimension and mitral valve excursion) were absent. Repeat echocardiography in 3 patients after pericardiocentesis showed increase in the left ventricular internal dimension, decrease in pericardial fluid and no respiratory change in left ventricular size or mitral valve excursion.

While the absence of PP in CT may not be specific for ASD, patients with significant, uncomplicated ASD who develop CT will not have PP, since the ASD allows for equalization of diastolic volumes and prevents respiratory changes in left ventricular volume that are associated with PP.

ADDENDUM

THE IMPACT OF REVASCULARIZATION SURGERY UPON HOSPITAL COSTS IN PATIENTS WITH ANGINA PECTORIS

John J. Collins, Jr., MD, FACC; William Y. Tucker, MD; Gary Kopf, MD; J. Kenneth Koster, Jr., MD; Roger B. B. Mee, MD; Lawrence H. Cohn, MD, FACC, Harvard Medical School, Boston, Massachusetts

This study compares the expense of revascularization surgery with the cost of continued medical management in patients with angina pectoris. A consecutive group of 102 patients with angina pectoris (excluding patients with predominant congestive heart failure, shock, and valvular heart disease) operated upon between April 1974 and April 1975 was selected for analysis. Hospitalizations for noncardiac illness and diagnostic angiography were excluded. There were 2 hospital deaths and no late deaths, leaving 100 patients whose course for 2 years before and 2 years after surgery could be compared. Within this group were 81 men, aged 28 to 68 ($\overline{50.1}$), and 19 women, aged 37 to 69 ($\overline{56.0}$). Significant obstruction was present in 3 or more vessels in 56 patients, 2 vessels in 36, and 1 vessel in 8. There were 35 patients receiving 3 grafts, 52 with 2 grafts, and 13 with 1 graft. During the 2 years before operation, 54 hospitalizations for cardiac problems were needed. There were 27 patients with 1 hospitalization, 17 with 2 admissions, and 10 with 3 or more admissions. In the 2 years after operation, there were only 10 hospitalizations for cardiac problems. Postoperative hospital days averaged 5.9 days/yr/pt fewer than during the 2 years prior to operation, representing an estimated saving of $2000/pt/yr. At this rate the $8000 average hospitalization cost for revascularization would be amortized in 4 years. These data suggest that coronary bypass may be a less expensive treatment than medical therapy for patients with severe angina pectoris.

VALVE REPLACEMENT IN CHILDREN AND ADOLESCENTS

Robert A. Mathews, MD; Sang C. Park, MD, FACC; William H. Neches, MD, FACC; Cora C. Lenox, MD,FACC; J.R. Zuberbuhler, MD, FACC; F. Jay Fricker, MD; Ralph D. Siewers, MD, FACC; Robert L. Hardesty, MD, FACC; David B. Lerberg, MD, Henry T. Bahnson, MD, FACC, Children's Hospital of Pittsburgh & University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Replacement of diseased heart valves has advanced over the past decade to become the treatment of choice in many adults. In children and adolescents, valve replacement has been used in our institution only when other surgical procedures are ineffective. Over the past ten years 27 patients have received 31 artificial valves. Thirteen patients (48%) had severe rheumatic valvular heart disease, many with two valve involvement. The remainder had congenital valvular aortic stenosis or insufficiency, congenital or acquired mitral insufficiency, absent pulmonic valve with tetralogy of Fallot or "corrected" transposition of the great arteries with left-sided A-V valve insufficiency. The Bjork-Shiley valve was used most frequently in the aortic position and the Beall prosthesis in the mitral position. There were eight deaths (30%); five immediately post-operatively and three within a year after surgery. Two children under age six and four undergoing double valve surgery died. The youngest survivor had valve replacement at 6½ years. Follow-up ranged from six to 79 months, averaging 30 months. All survivors returned to normal activity and are free of cardiac symptoms Hemarthrosis secondary to anticoagulation was seen in three patients (11%).

Our experience in the pediatric age group suggests that valve replacement can be performed at higher risk than the adult but at reasonable risk for those patients in whom valvulotomy or valvuloplasty is expected to be ineffective

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President's Page

Reflections on Progress Achieved and Future Challenges

Dr. Mason

Now that my Presidency nears completion (according to my calendar), analysis of events during the past 12 months and of issues emerging ahead clearly indicates to me that this responsibility is an accelerating continuum, not unlike running in a relay race. With only the date signalizing the end of my term, which began in Las Vegas one year ago, it is appropriate and desirable that I pass on the ton to my worthy successor Dr. Leon rd Dreifus, who is already in full stride. I can sincerely attest that leadership of the College constitutes total involvement and promises to do so with increasing intensity for several years to come.

As the complexity of all aspects of cardiovascular patient care and research continues to grow exponentially, as well as the multiplicity of influences upon them by forces from inside and outside the profession, the College President no longer conducts a one-person show. Rather, the process of decision making and guidance comprises a consortium of dedicated dynamic officers, membership and staff. While the ultimate responsibility as prime spokesman of the College necessarily belongs to the President, he aims at policy statements that are determined by consensus of the Board of Trustees acting upon the advice of College Committees and Governors, who represent the entire membership. Importantly, our organizational structure, based upon the concept of shared leadership, provides the process of rapid response and flexibility that characterizes the principal strength of the College in the thoughtful formulation of advancements and innovations for improved high quality care of patients with heart disease.

Although sometimes nearly energy-spent, I have found the year as your President highly satisfying and rewarding. Not only has there been a succession of invaluable personal experiences, but also I believe it has been a landmark year of salutary College developments. Most noteworthy is the establishment of a permanent home for the College—Heart House in Bethesda, Maryland. Learning Center cardiovascular programs in continuing education and in educational research are already operational at Heart House, and our extramural cardiovascular symposia enjoy widespread popularity nationally, as does our ACCEL audio tape journal.

In addition, through the activities of Dr. Charles Fisch and his committee, the goals and objectives of the college have been delineated and formally approved by the membership. Our program of Bethesda Conferences continues to flourish; the Conference on Optimal Electrocardiography was a major achievement, and plans are underway for conferences on emergency cardiovascular care systems and on the prevention of coronary artery disease. Furthermore, the total College membership has grown to well above 8,000 cardiovascular specialists and our Journal has become the leader in the discipline with over 21,000 subscribers. Moreover, the forthcoming 27th Annual Scientific Session of the College in Anaheim on March 6 to 9 is the most expansive educational and cultural program yet formulated by the College and a record attendance is anticipated.

Equally significant have been the closer and more meaningful relationships the College has developed with components of the federal government dealing with health care legislation and regulations: the National Institutes of Health (NIH); the National Library of Medicine; other medical professional groups and voluntary health societies whose members provide cardiovascular care (such as the Interspecialty Advisory Board of the American Medical Association, the Council of Subspecialty Societies of the American College of Physicians, the American Heart Association, and the American Academy of Family Physicians); and the Subspecialty Board on Cardiovascular Disease of the American Board of Internal Medicine. Especially noteworthy have been our recommendations, provided at the invitation of the Senate and the House, concerning renewal legislation and budget for the National Heart, Lung, and Blood Institute (NHLBI), and the recommendations requested by the Food and Drug Administration, Health Systems Agencies and the Health Resources Administration.

Of particular importance to our membership has been the College's recent forceful response to the proposed National Guidelines for Health Planning by the Health Resources Administration published in the September 23, 1977 Federal Register. In this regard, it is anticipated that our strong recommendations comprising extensive constructive revisions concerning potential rule-making affecting cardiac catheterization unit services and open heart surgery will have a major influence on any revised guidelines that may be published.

The College has become the foremost professional specialty society in cardiology and has rightfully earned its credibility in this leadership role as the principal active spokesman for the American

physician specializing in cardiovascular disease. Furthermore, as a society composed of practitioners, scientists and educators, the College stands ready and able to participate in the formulation of social, economic and legislative goals that reflect national trends in attitudes and priorities in cardiovascular medicine. In carrying out our responsibility for bringing new ideas and concepts to cardiovascular medicine, we must continue to evaluate thoroughly the implementation of our mission within the carefully established goals and objectives of the College.

Crucial decisions and important challenges are foreseen both within the activities of the College and in the relation of the broad scope of cardiology to medicine and society in general. I have addressed some of these issues in previous President's Pages in this Journal, especially in "Insights and Directions" (April 1977), "Preventive Cardiology" (May 1977), "Government Relations" (June 1977), "International Education" (August 1977), "Continuing Educational Research" (November 1977) and "Departments of Cardiovascular Disease" (December 1977).

In addition, the College has its attention focused on the difficult problem of diminishing support for cardiovascular research and the training of future investigators in this field. Whereas cardiovascular diseases account for nearly one million deaths annually in the United States and 51 percent of all mortality nationally, less than 10 percent of NIH funds are designated for cardiovascular research. Moreover, considering the total NHLBI budget alone, the percent allowed for cardiovascular research has decreased drastically over the past decade from 73 to only 57 percent. Clearly a greatly expanded federal program for the support of research on heart and blood vessel diseases should be given primary national priority.

Finally, I take this opportunity to express my great appreciation to the many persons who have provided me with outstanding support during my year as your President. Space is insufficient to name everyone. Nevertheless, I would be lacking in gratitude without specially thanking at least a few who have been absolutely invaluable: William Nelligan; Dr. Anthony DeMaria; Leslie Silvernail—my Executive Manager; and my wife Maureen and daughters Kathleen and Alison, whose love and understanding made it all possible.

Dean T. Mason, MD, FACC
President 1977–78
American College of Cardiology

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education.

Each continuing education program is directed toward a specific target group including: adult cardiologists (CD), internists (IM), pediatric cardiologists (PDC), and family practitioners (FP). For additional information concerning the programs listed below or for a complete schedule of programs through October 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

MARCH THROUGH MAY 1978

Mar. 27–30 **Congestive Heart Failure: A Changing Scene? (CD) (IM).** Charles B. Mullins, MD, FACC, director

Apr. 3–6 **Cardiac Emergencies: Recognition and Therapy (CD) (IM).** Charles E. Rackley, MD, FACC, director

Apr. 10–12 & 13–15 **Adult Echocardiography: Clinical Applications and Recent Advances (CD) (IM).** Pravin M. Shah, MD, FACC, director

Apr. 17–20 **Pediatric Echocardiography (PDC).** Richard A. Meyer, MD, FACC, director

Apr. 24–26 **Exercise Testing: Diagnostic and Physiologic Considerations (CD) (IM).** Keith Cohn, MD, FACC, director

MAY 8–10 & 22–24 **Electrocardiography of Arrhythmias (IM).** Charles Fisch, MD, FACC, director

MAY 15–18 **Update in Cardiology (CD).** R. Joe Noble, MD, FACC, director

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

FEBRUARY 1978 THROUGH MAY 1978

To be arranged individually **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

FEB. 3–5 **Management of Cardiac Diseases—1978.** Robert J. Myerburg, FACC and Agustin Castellanos, FACC, co-directors. Omni International Hotel, Miami, FL

FEB. 23–25 **Advances in the Diagnosis and Therapy of Cardiovascular Disease—1978.** John Ross, Jr., FACC, Joel S. Karliner, FACC, Ralph Shabetai, FACC, Kirk L. Peterson, FACC and Allen D. Johnson, FACC, co-directors. Hotel del Coronado, Coronado, CA

MAR. 3–4 **Complex Problems in Congenital Heart Disease.** Robert M. Sade, FACC and Arno R. Hohn, FACC, co-directors. Kiawah Island Inn, Charleston, SC

MAR. 6–9 **Twenty-seventh Annual Scientific Session.** Dean T. Mason, FACC, president. Anaheim Convention Center and Disneyland Hotel, Anaheim, CA

MAR. 10–11 **Post Anaheim, California. Symposium on Clinical Cardiology.** Anthony N. DeMaria, FACC, director. Kauai Surf Hotel, Kauai, HI

MAR. 27–31 **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

MAR. 30–APR. 1 **Contemporary Management of Acute Myocardial Infarction by the Family Physician.** Robert S. Eliot, Chairman and Ernie J. Chaney, Alan D. Forker, Harold Kalman and Thomas Nicholas, program committee. Sarasota Hyatt House, Sarasota, FL

APR. 3–7 **Consultant's Course in Cardiology.** Michael V. Herman, FACC, director and Simon Dack, FACC, Richard Gorlin, FACC and Louis E. Teicholz, FACC, co-directors. Mount Sinai Medical Center, New York, NY

APR. 3–12 **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 12–14 **Vectorcardiography: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 19–21 **Echocardiographic Solutions to Clinical Cardiovascular Problems.** Joseph K. Perloff, FACC and John S. Child, FACC, directors. Century Plaza Hotel, Los Angeles, CA

MAY 8–10 **The Physiologic Basis for Diagnosis and Treatment of Heart Disease—A Tribute to William Harvey on his 400th Birthday (1578–1657).** J. Willis Hurst, FACC, director and Robert C. Schlant, FACC, co-director. Colony Square Hotel, Atlanta, GA

MAY 12–14 **Rational Drug Therapy in Ischemic Heart Disease.** Robert J. Lee, director, Palmer House, Chicago, IL

MAY 12–15 **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

MAY 18–20 **Cardiovascular Nuclear Medicine and Comparative Techniques: 1978.** Lawrence S. Cohen, FACC, Alexander Gottschalk, Barry L. Zaret, FACC, directors. Yale University School of Medicine, New Haven, CT

AMERICAN COLLEGE OF CARDIOLOGY

Announces . . .

AFFILIATE MEMBERSHIP

For Physicians in Cardiovascular Related Training Programs

This membership category is open to all Fellows in cardiovascular (adult, pediatric, surgical, etc.) training programs. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

The application for Affiliate (in Cardiovascular Related Training) must be signed by the Director of the applicant's training program and two sponsors, both of whom must be Fellows of the College. One of the sponsors may be the Director of the training program, provided he is a Fellow of the College. The annual dues for an Affiliate (in Cardiovascular Related Training) are $20.00 (U.S.).

Advantages to the Affiliate (in Cardiovascular Related Training)

1. Subscription to *The American Journal of Cardiology*, the official journal of the College.
2. Reduced fees for all educational programs of the College.
3. Preference for enrollment in programs sponsored by the College with a limited registration.
4. Receipt of the quarterly publication, *Cardiology*, the newsletter of the College.
5. Participation in all affairs of the College as a member rather than as a guest of the College.

Those desiring an application form should write to Ms. Margaret E. Coffey, Director, Membership Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

INSTRUCTIONS FOR AUTHORS

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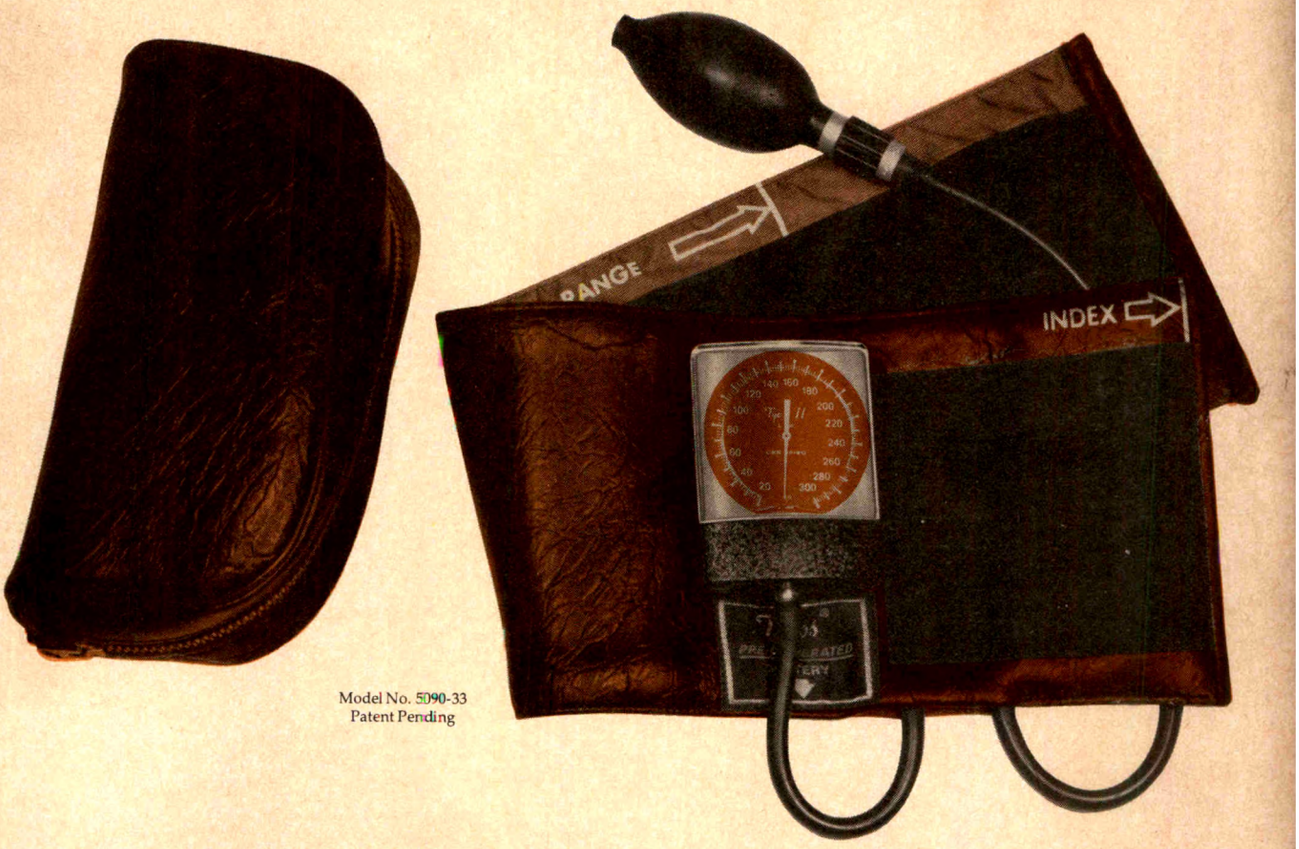

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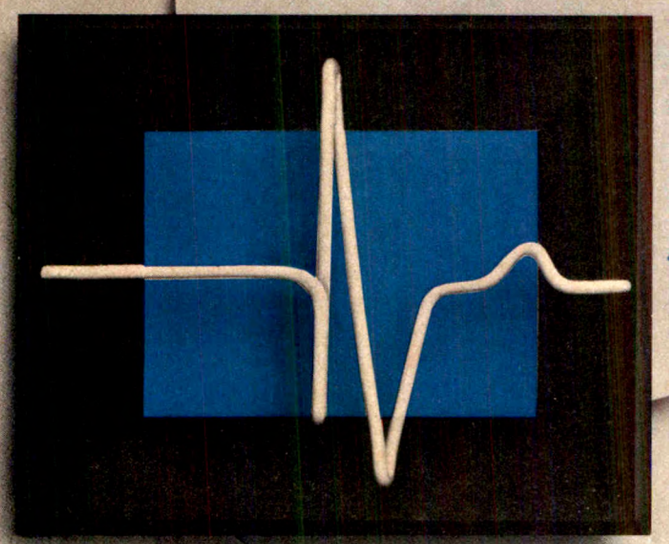

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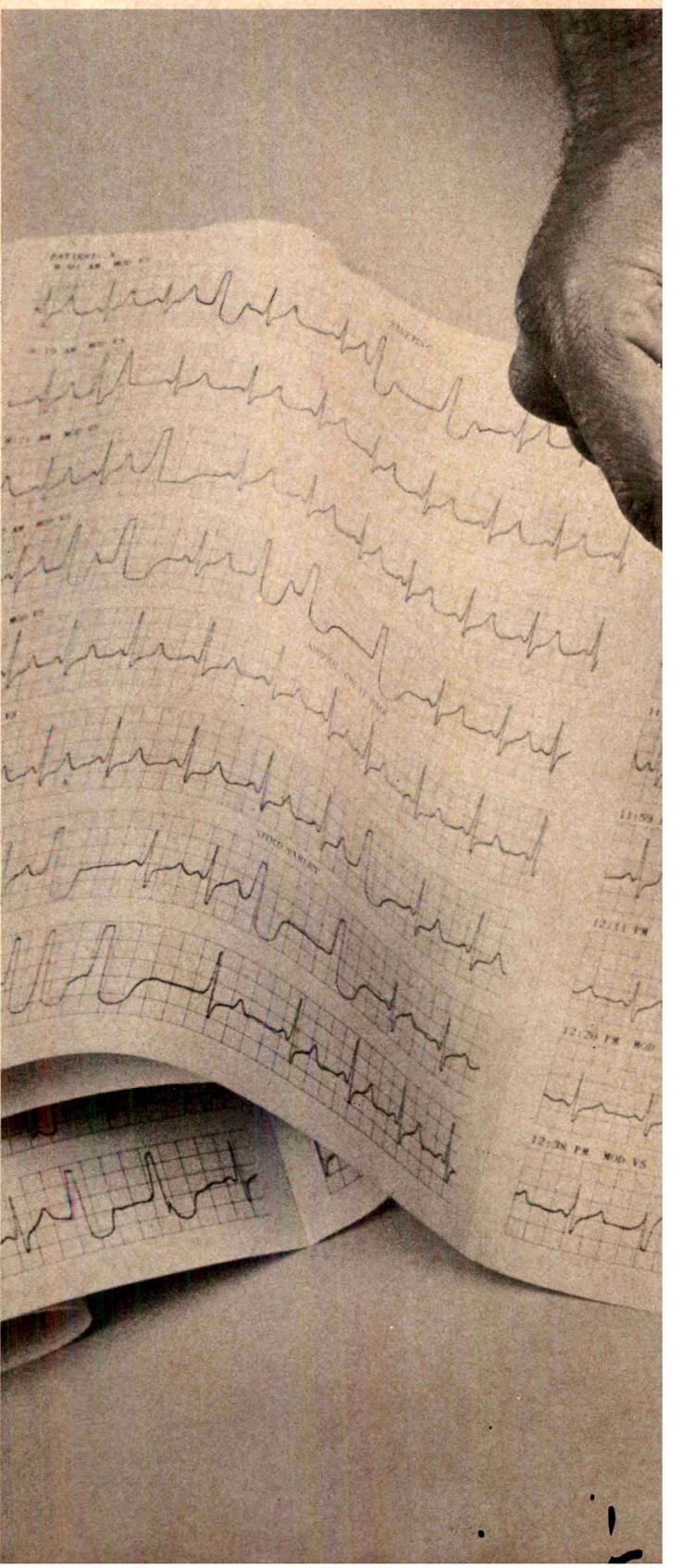

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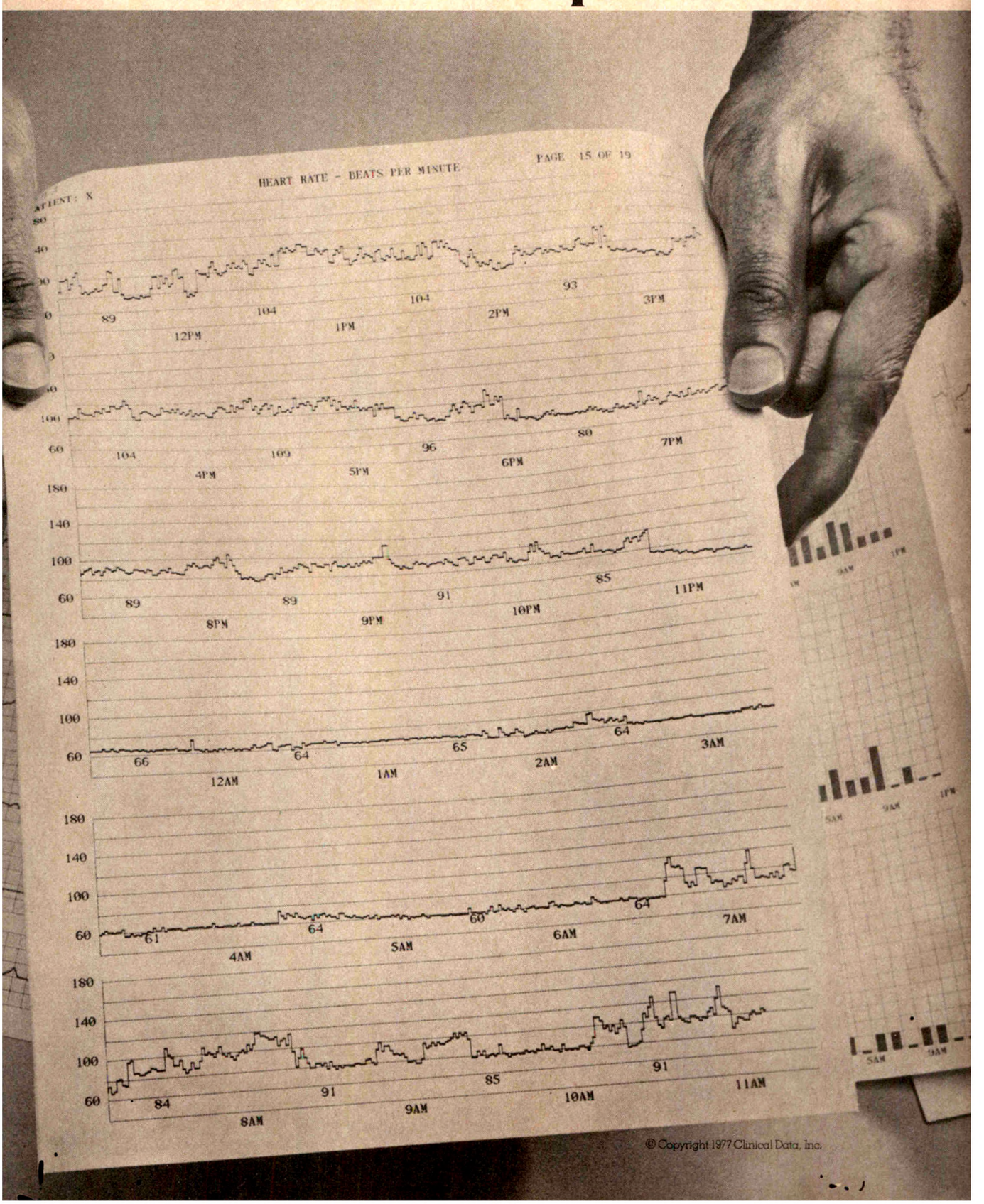

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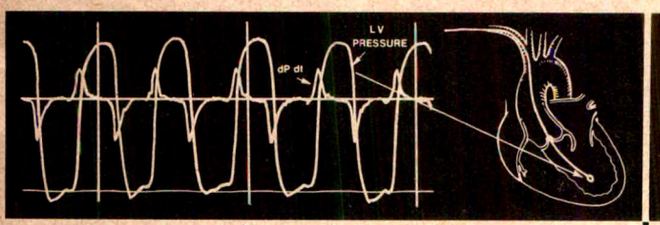

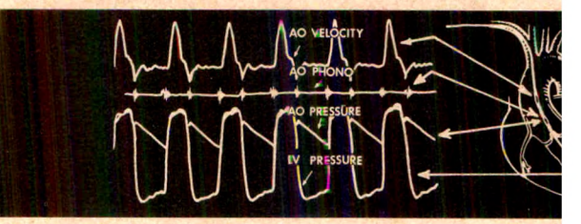

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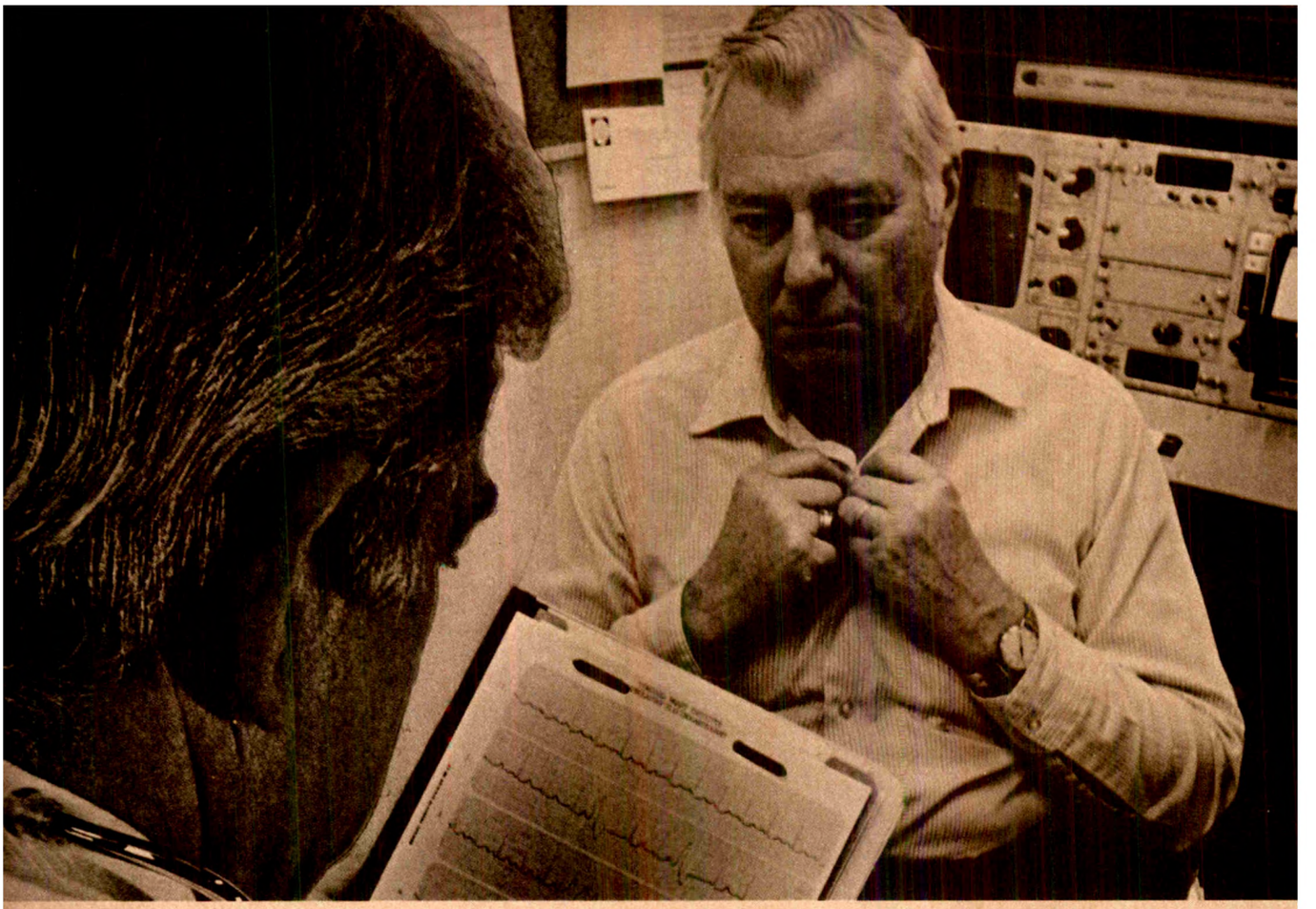

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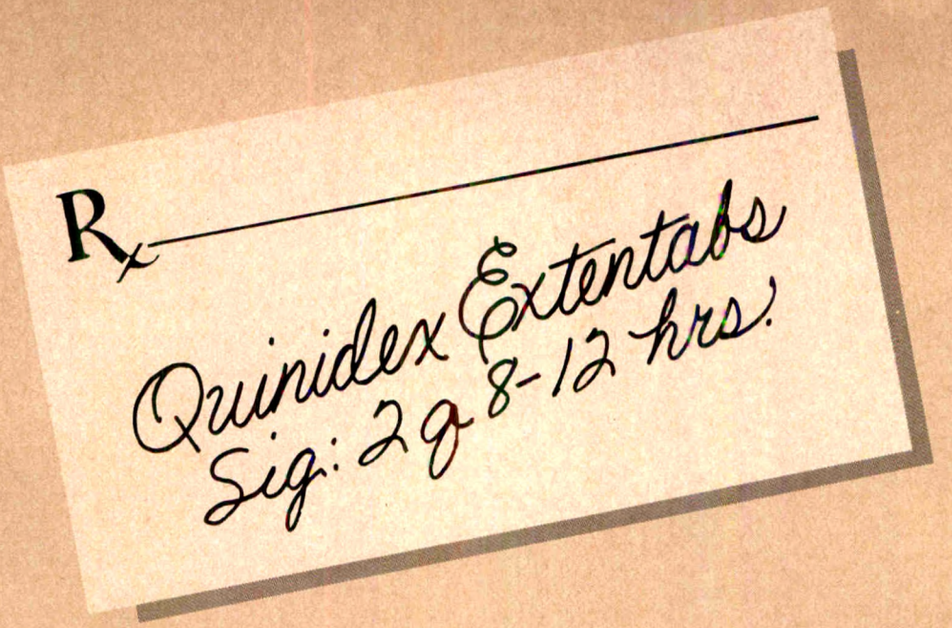

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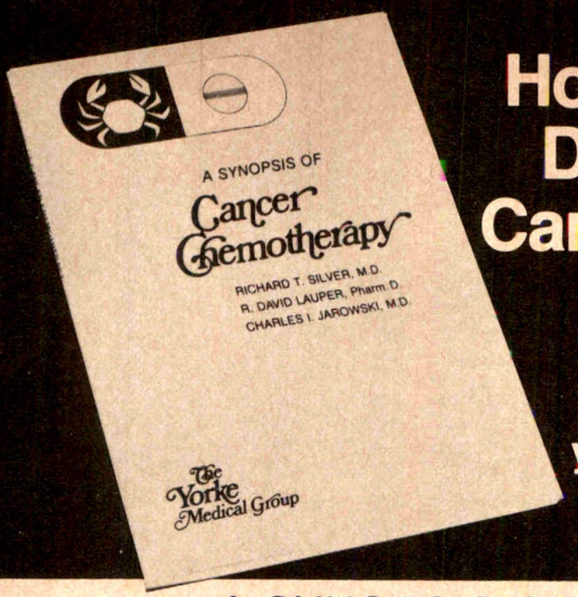

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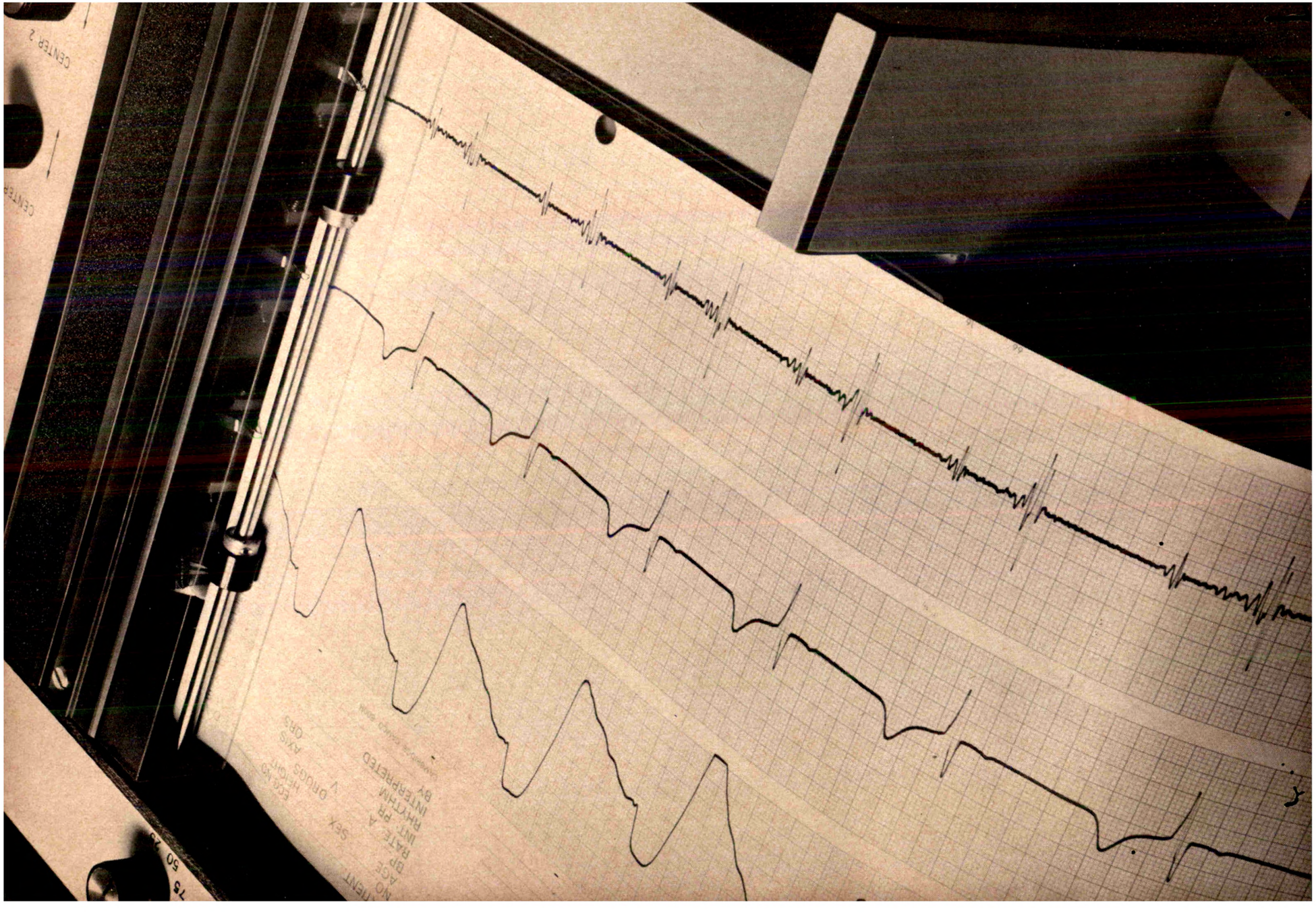

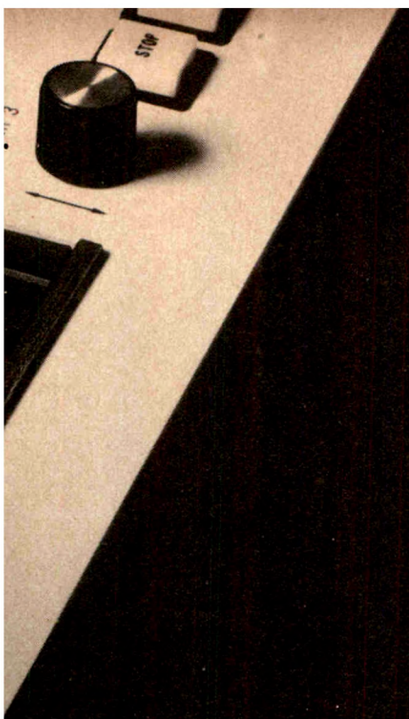

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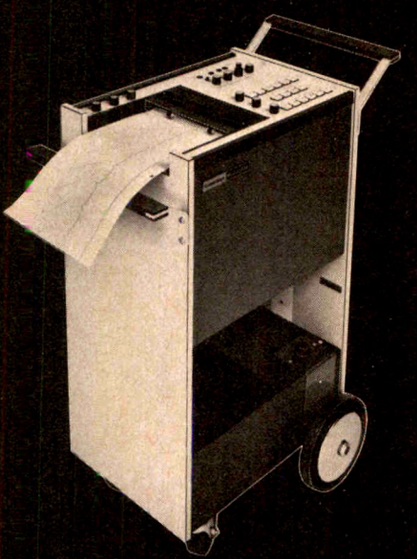

Best yet, this three-channel workhorse packs cost/efficiency benefits that can actually save its cost in just one year of use. Where conventional three-channel ECG's use up to 100% more paper for the blank run-out "gap" between recordings, Model 3038's no-waste design makes the electrocardiogram immediately visible without paper loss. What's more, pre-printed patient data and notation headings make it easy to write or type data at once for a single-sheet, file-folder size record requiring no time, labor or material expense for cutting or mounting.

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Model 3038 offers three recording modes plus an observe mode, recording logic programmability, and optional computer compatibility. A drop-in paper-loading feature even eliminates winding and threading. Double insulated for safety, it is designed to meet or exceed all American Heart Association standards. But why stop there? To see how it suits *your* needs best, write or call: Cambridge Instrument Company, Inc., 73 Spring St., Ossining, N.Y., (914) 941-8100.

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Specific new approach to cholesterol lowering.

LORELCO is unrelated chemically to any other cholesterol-lowering agent presently available.

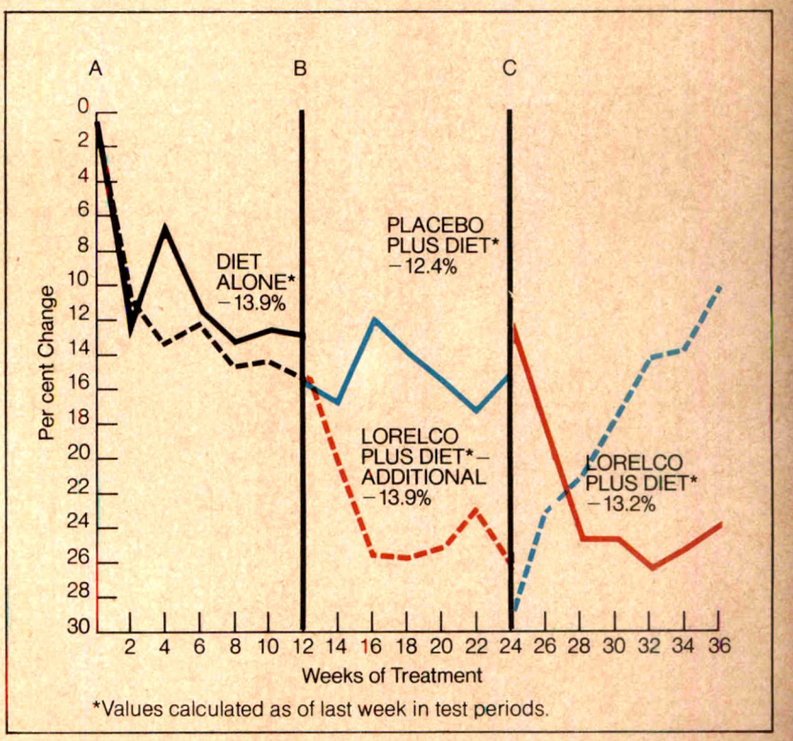
LORELCO, in combination with diet, yields significant reductions in serum cholesterol.†

As indicated in the figure at right:

☐ At point A, patients in two groups were placed on a diet low in cholesterol and saturated fat.

☐ At point B, one group of patients (red line) was started on therapy with LORELCO, two 250 mg. tablets twice daily, in addition to diet. Over the next 3 months, this group showed further reduction in serum cholesterol, significantly below that achieved with diet alone. The other group (blue line) received placebo while diet therapy was continued. No additional reduction in serum cholesterol levels was noted.

☐ At point C, the two groups were crossed over. Serum cholesterol levels increased rapidly when the group formerly receiving LORELCO was given placebo. Conversely, a sharp reduction in serum cholesterol occurred in the group given LORELCO instead of placebo.



*Values calculated as of last week in test periods.

†J. LeLorier, S. Dubreuil-Quidoz, S. Lussier-Cacan, Y.S. Huang and J. Davignon, Clinical Research Institute and University of Montreal: "Diet And Probucol In Lowering Cholesterol Concentrations." Archives of Internal Medicine, Vol. 137, October 1977

Sustained reduction in serum cholesterol.

In long-term studies of 882 patients on various diets, regardless of fat or cholesterol content, 315 were maintained on LORELCO over a period exceeding four years. A significant reduction in mean serum cholesterol levels in that group was sustained throughout the study.

It's well-tolerated.

Diarrhea, the most common side effect occurred in about one patient in ten. Treatment was discontinued in about one patient in thirty because of side effects, mainly gastrointestinal disturbances.

It's convenient for your patients.

LORELCO offers convenient twice-a-day dosage. There's no noon-time dose to remember or forget. No inconvenient mixing or stirring.

Special note.

LORELCO is metabolized and excreted over a period of months. LORELCO is not recommended for use during pregnancy or in women contemplating pregnancy within 6 months.

LORELCO
PROBUCOL

Chart the course that's specific.

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Dow Pharmaceuticals
The Dow Chemical Company
Indianapolis, Indiana 46268

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Current investigations now in progress may yield an answer to this question.

See complete product information on next page.

A147

LORELCO
PROBUCOL

Chart the specific course in cholesterol therapy. 2 tablets b.i.d.

DESCRIPTION:
LORELCO (probucol) is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-(isopropylidenedithio) bis (2,6-di-t-butylphenol). Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.

CLINICAL PHARMACOLOGY:
The pharmacological mode of action by which LORELCO lowers serum cholesterol levels is unknown. However, there is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis it is concluded that LORELCO does not affect the later stages of cholesterol biosynthesis.

Absorption of LORELCO from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter, remain fairly constant.

At the end of 12 months of treatment in eight patients, blood levels averaged 19.0 μg/ml and ranged from 7.3 to 29.8 μg/ml. Six weeks after cessation of therapy, the average had fallen 60 per cent to 7.8 μg/ml (range from 3.2 to 16.3 μg/ml). After six months the average had fallen 80 per cent to 3.6 μg/ml (range from 1.5 to 6.0 μg/ml).

INDICATIONS AND USAGE:
Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long term use.

LORELCO is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins). LORELCO may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Current investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS (See also precautions):
LORELCO is contraindicated in patients who are known to have a hypersensitivity to it.

PRECAUTIONS:
Before instituting therapy with LORELCO an attempt should be made to control serum cholesterol by appropriate dietary regimens, weight reduction, and the treatment of any underlying disorder which might be the cause of the hypercholesterolemia.

Because LORELCO is intended for long-term administration, adequate baseline studies should be performed to determine that the patient has elevated serum cholesterol levels. Serum cholesterol levels should be determined frequently during the first few months of treatment and periodically thereafter. A favorable trend in cholesterol reduction should be evident during the first two months of probucol administration. The regimen should be followed as long as the trend continues. A decision should be made by the sixth month whether adequate reduction is being attained.

A baseline for serum triglycerides should also be established and serum triglyceride levels should be determined periodically. If a marked sustained rise in serum triglycerides is observed during probucol therapy, consideration should be given to improved diet compliance, alcohol abstinence, further calorie restriction or adjustment of carbohydrate intake. LORELCO (probucol) should not be continued if hypertriglyceridemia persists.

Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of LORELCO on serum cholesterol. The dosage of these agents is not usually modified when given with LORELCO.

Use in Pregnancy: Reproduction studies have been performed in rats and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to LORELCO. Because there are no adequate studies in pregnant women, use of this drug in pregnancy is not recommended. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn, and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See Clinical Pharmacology.)

Use in Nursing Mothers: It is not known whether this drug is excreted in human milk, but it is likely to be since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on LORELCO.

Use in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:
The adverse reactions associated with LORELCO are generally mild to moderate and of short duration.

The most commonly affected system is the gastrointestinal tract. Diarrhea occurs in about one in 10 patients. Other adverse gastrointestinal reactions in descending order of frequency are: flatulence, abdominal pain, nausea and vomiting. These reactions are usually transient and seldom require the drug to be discontinued. During the clinical studies, LORELCO was discontinued in about 2 per cent of the patients because of adverse gastrointestinal reactions.

Less frequent adverse reactions are: hyperhidrosis, fetid sweat and angioneurotic edema which were reported in less than one in 500 subjects.

An idiosyncratic reaction characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain has been reported.

Other events have been reported in patients treated with LORELCO. The relationship between these events and probucol is not well established. In this group are included totally subjective complaints which are attributed to drugs even though many individuals have symptoms of this sort in the absence of drug ingestion. Also included are events which could have been produced by the patient's state or other modes of therapy. The most frequent were headaches, dizziness, paresthesias and eosinophilia observed in about one of each 50 subjects. Consistently low hemoglobin and/or hematocrit values were observed in about one of each 100 patients. Less frequent were: rash, pruritus, impotency, insomnia, conjunctivitis, tearing, blurred vision, tinnitus, diminished sense of taste and smell, enlargement of a multinodular goiter, anorexia, heartburn, indigestion, gastrointestinal bleeding, ecchymoses and petechiae, decreased hemoglobin, thrombocytopenia, nocturia, and peripheral neuritis. These were observed in the range of one to six per thousand subjects.

Elevations of the serum transaminases (glutamic-oxalacetic and glutamic-pyruvic), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen and blood glucose above the normal range were observed on one or more occasions in various patients treated with LORELCO. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between probucol and these abnormalities is not firm, the possibility that some of these are drug related cannot be excluded. In the controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with probucol than in the patients who received placebo.

DOSAGE AND ADMINISTRATION:
For adult use only. The recommended dose is 500 mg (2 tablets of 250 mg each) twice daily with the morning and evening meals.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:
Each film-coated tablet contains 250 mg probucol and is imprinted with the DOW diamond trademark over the code number 51.

Bottles of 120 tablets, a 30-day supply for one patient (NDC 0183-0051-26). Unit dose packages of 112 tablets (NDC 0183-0051-71).

Keep well closed. Store in a dry place, avoid excessive heat and dispense in light-resistant containers.

ANIMAL PHARMACOLOGY AND TOXICOLOGY:
From studies in rats, dogs and monkeys it is known that probucol accumulates slowly in adipose tissue. Approximately 90 per cent of probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body. After a single dose approximately 10 per cent of the absorbed drug was recovered from bile collected from rats over a period of 30 hours. Very little is excreted by way of the kidneys. Following a single intravenous injection in rats, only one per cent of the drug was recovered in the urine over a 24-hour period.

Probucol has shown no identifiable toxicity in mice, rats and monkeys. In mice and rats the LD_{50} (oral) is in excess of five grams per kilogram of body weight. Two-year chronic toxicity studies in rats and a study in monkeys exceeding seven years in duration have shown probucol to be without adverse effect.

During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles), there were 12 fatalities. The behavior, physical condition, laboratory findings and post-mortem evaluations were considered to be within normal limits.

Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine resulting in ventricular fibrillation in many dogs.

Among the animal species in which probucol has been studied, the dog is peculiar with respect to the phenomenon of sudden death and the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation. In other studies, monkeys were given probucol either before and after, or only after myocardial infarction induced by coronary artery ligation. In these studies there was no difference between probucol and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probucol was administered to minipigs beginning 10 days before ligation of a coronary artery and continued for 60 days post surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary ligated, probucol-treated minipigs.

In summary, probucol is toxic to the dog; the target organ is the heart. This phenomenon appears to be unique to the dog. Toxic effects were not identified in four other species.

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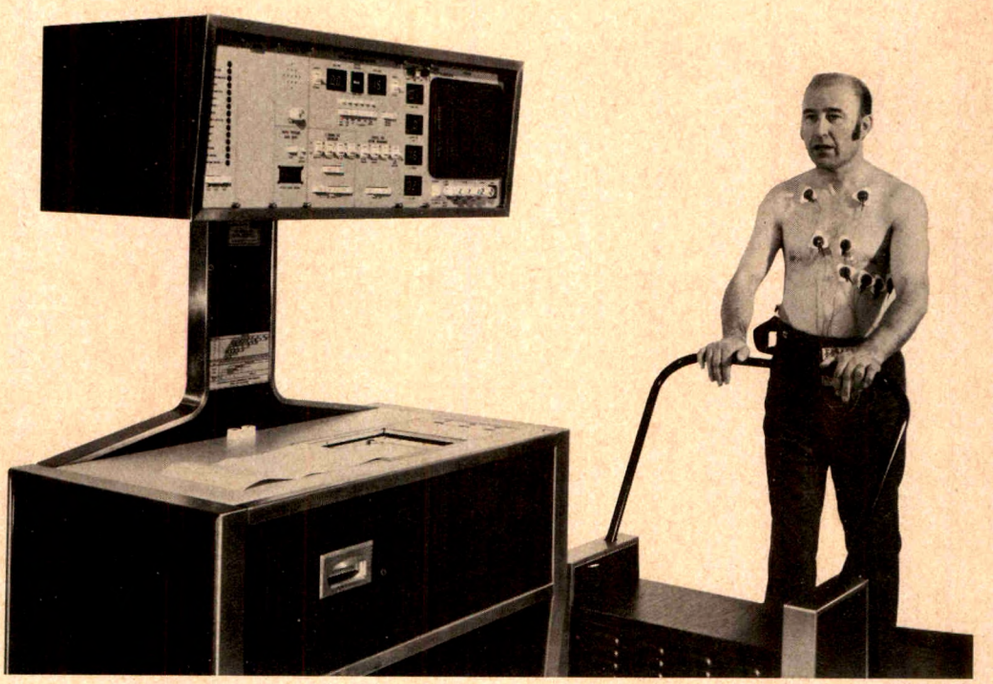

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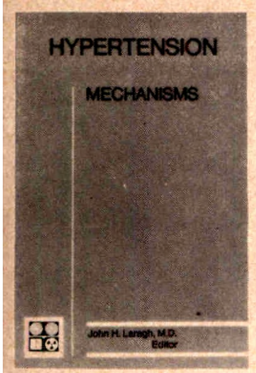

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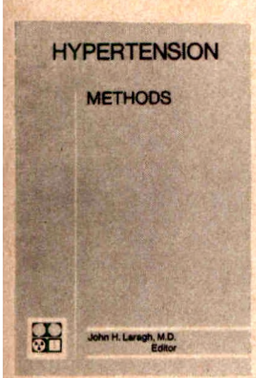

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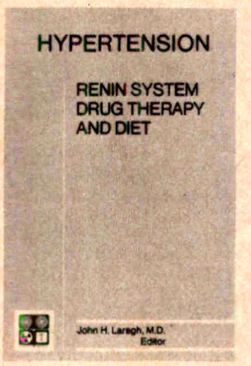

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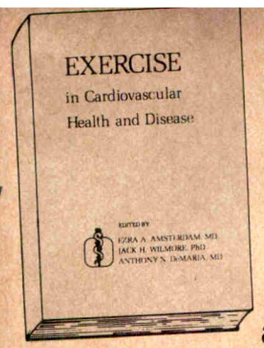

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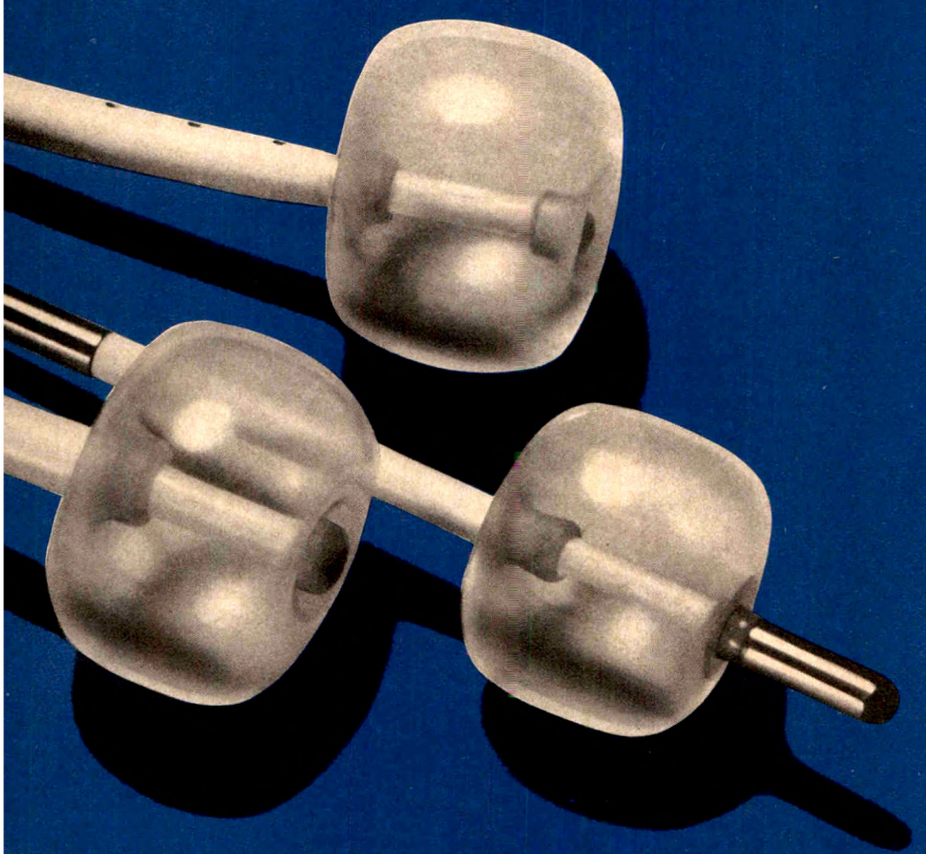

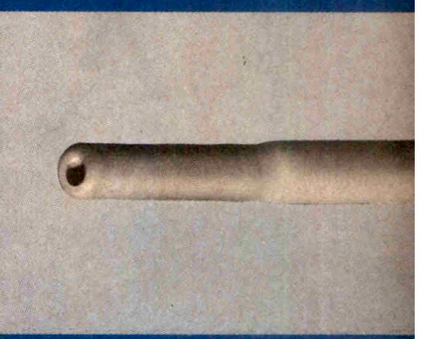

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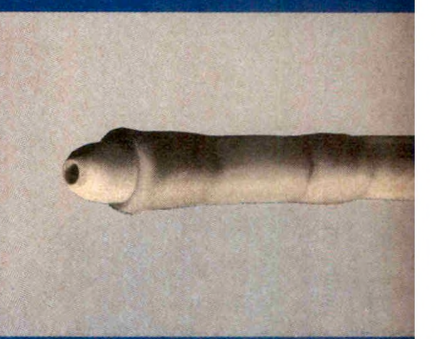

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As you can see, the Extracorporeal tip is smooth, tapered, unruffled, suture free, no wider than the catheter itself. The benefits are built-in:

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- **Less blood is lost.** Because the introducer is smaller and because the catheter fits it snugly the entire length of the catheter.
- **Our tapered tip has a larger lumen** which reduces the likelihood of clotting and makes it easier to introduce drugs and dyes.
- **A smaller diameter catheter may be used,** because a larger lumen also produces pressure measurements of a fidelity that can usually be matched only by a larger-diameter competitive catheter.
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Beyond the tip, a host of other benefits.

- **Inflation is more convenient** because every Extracorporeal balloon catheter is packaged with an appropriately sized syringe.
- **Pure platinum electrodes for better electrical characteristics.** Blood may alter the conductivity properties of stainless steel and cause inferior readings. That's why our balloon pacing catheters employ only inert platinum for electrodes.
- **High pressure tubing** used in our Berman angiographic catheters permits higher pressures to be used to achieve better flow rates when drugs or dye must be injecte
- **More sizes available.** Especially in Berman angiographic and wedge pressure models. And we can supply custom catheters, too.
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*With one small exception—the Extracorporeal 4F size uses a 4-1/2 size introducer.

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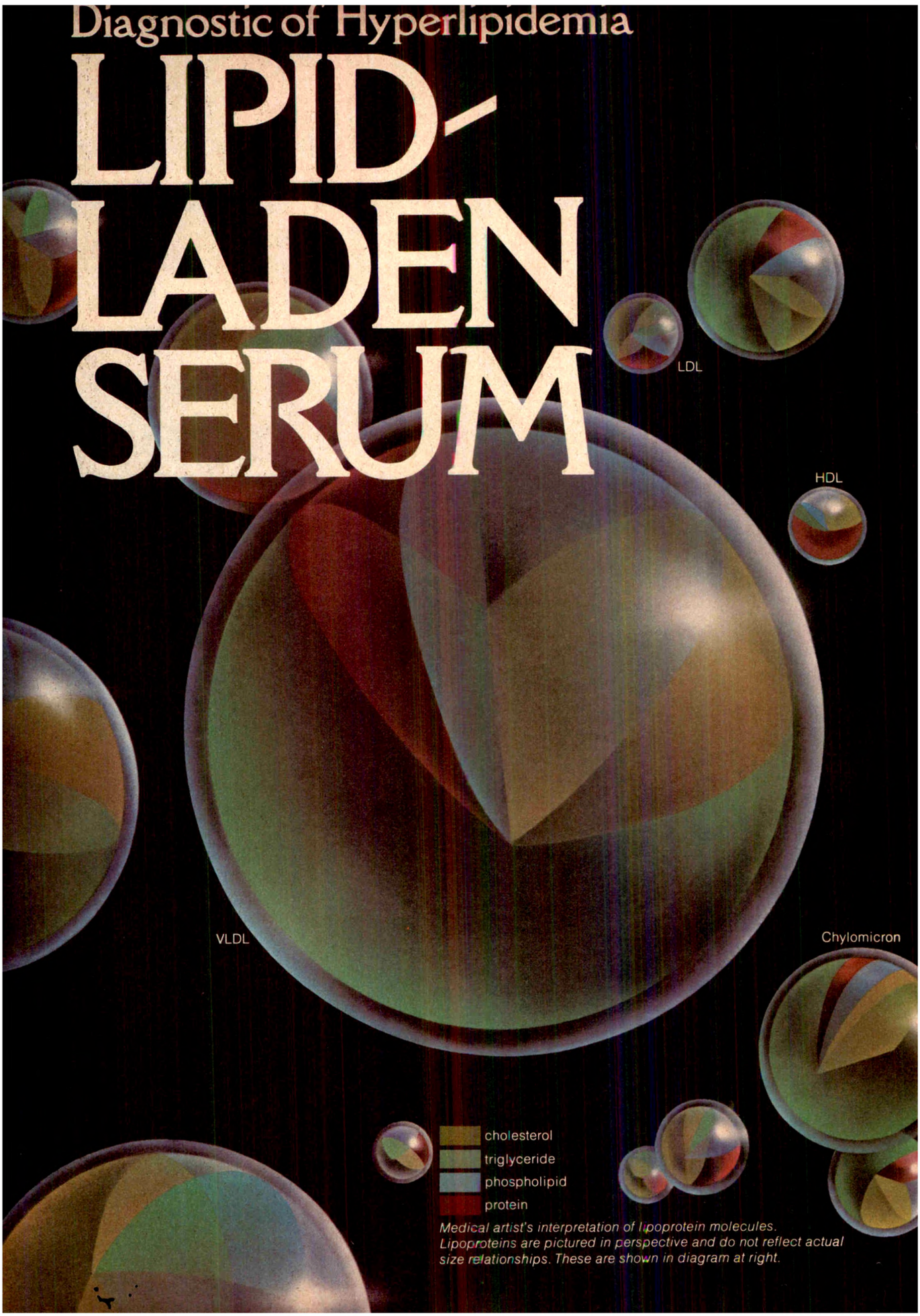
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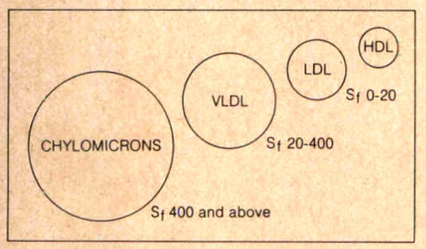
HDL
VLDL
Chylomicron
cholesterol
triglyceride
phospholipid
protein
Medical artist's interpretation of lipoprotein molecules. Lipoproteins are pictured in perspective and do not reflect actual size relationships. These are shown in diagram at right.

Lipoproteins: The "cargo" and the "transport vehicle"

Since fats are insoluble in water, they must link up with protein to remain dispersed in the blood. The lipoprotein molecules thus formed allow lipid substances—cholesterol, triglycerides, phospholipids—to travel freely in a soluble form through the bloodstream for use as structural building blocks and sources of energy. The four major classes of lipoprotein, consisting of varying amounts of lipids (the "cargo") and protein (the "transport vehicle") are chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). [See medical artist's interpretation at left.] The relative size of these lipoprotein molecules, based on measurement of flotation rates via ultracentrifugation, is shown below.

SCHEMATIC RELATION OF SIZE TO FLOTATION RATE (S_f)



Abnormalities in the production and/or degradation of these lipoproteins can lead to excessive accumulations of cholesterol and/or triglycerides in the serum. These elevations in serum lipids, in the absence of underlying causative disease, are diagnostic of hyperlipidemia.

Early intervention—a rational approach to the management of hyperlipidemia

Reducing elevated lipid levels is a rational therapeutic goal at any point in the hyperlipidemic process—but is perhaps most logical in the early stage. This is the stage when most patients are asymptomatic, yet routine cholesterol and triglyceride determinations will disclose that nevertheless they are hyperlipidemic.[1]

If persistent, clinically significant lipid elevations are demonstrated—and underlying disease states are ruled out through history, physical examination, and appropriate laboratory tests—a diagnosis of primary hyperlipidemia is confirmed.

Dietary modification directed at correcting the specific lipid abnormality should be instituted as the first therapeutic step, but it often fails to lower the lipids sufficiently.

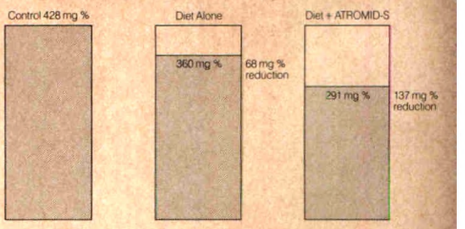
This is the best time to add ATROMID-S an antilipidemic agent, to the regimen. Early, effective, and continuous lipid lowering is important in the successful management of hyperlipidemia.

When diet alone is not enough, Atromid-S can further reduce elevated serum lipids

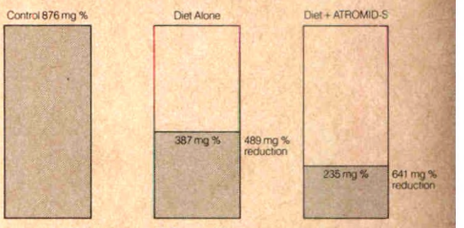
As an adjunct to diet and other measures, ATROMID-S depresses levels of both the very low density lipoproteins (S_f 20-400) and the low density lipoproteins (S_f 0-20), with an apparently greater effect on the former. The result of these actions is a reduction in elevated serum cholesterol (particularly the cholesterol carried by LDL) and/or triglycerides.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

ATROMIDS-S Lowers Cholesterol Significantly Better Than Diet Alone
Results in 7 patients with hypercholesterolemia
Mean Difference mg %*



ATROMIDS-S Lowers Triglycerides Significantly Better Than Diet Alone
Results in 7 patients with hypertriglyceridemia
Mean Difference mg %*



*Adapted from Brown, H.B., *et al.*[2]

Continuous therapy and constant dosage essential to long-term control

Lipid lowering is sustained as long as ATROMID-S treatment is uninterrupted. However, if the drug is stopped, lipid levels may return to or above pretreatment levels.

ATROMID-S is effective in a simple, well-accepted regimen. Initial *and* maintenance dosage is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

As an adjunct to diet

Atromid-S®

Brand of

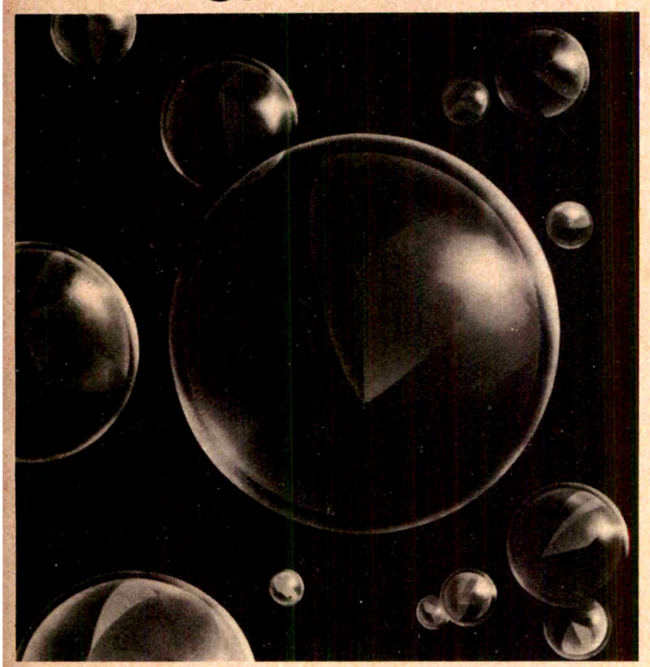
clofibrate

Helps reduce elevated serum levels of cholesterol and/or triglycerides

See last page of this advertisement for prescribing information.

Atromid-S® (clofibrate)

Helps reduce elevated serum levels of cholesterol and/or triglycerides



BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

References: 1. Scheig, R.: Conn. Med. 39:71 (Feb.) 1975. **2.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. 17:171 (Feb.) 1975.

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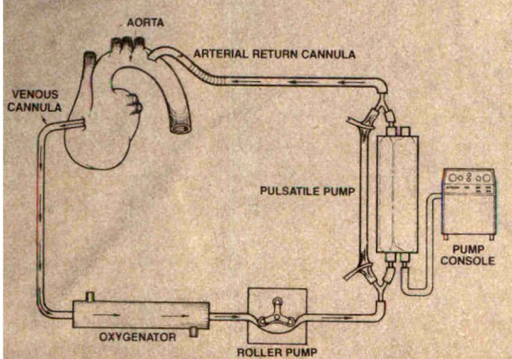

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LASIX® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide).

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs. Patients not adequately controlled with thiazides probably will not be adequately controlled with furosemide.

Contraindications: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. Continued use if increasing azotemia and oliguria occur during treatment of severe progressive renal disease. Hepatic coma. Electrolyte depletion. History of hypersensitivity to the compound.

Warnings: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Perform frequent serum electrolyte, CO_2 and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. **Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital.** Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions.

Precautions: As with any potent diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Since furosemide potentiates the effect of antihypertensive medications, reduce the dose of these agents when furosemide is administered to edematous hypertensive patients. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Cases of tinnitus and reversible hearing impairment have been reported when parenteral furosemide therapy preceded oral use. There are also reports of irreversible hearing impairment. Usually, ototoxicity has been reported when doses of furosemide exceeding several times the usual recommended dose were injected rapidly in patients with severe impairment of renal function who were also often receiving other drugs known to be ototoxic. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, it has been reported that an infusion rate not exceeding 4 mg furosemide per minute has been used.) Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Exercise great caution in administering curare or its derivatives to patients undergoing furosemide therapy, and it is advisable to discontinue furosemide for one week prior to any elective surgery.

Adverse Reactions: Various forms of dermatitis, urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea. Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis, which responded to treatment. Although relationship to the drug has not been established with certainty, the following rare adverse reactions have been reported: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli, and acute pancreatitis. Furosemide-induced diuresis may be accompanied by weakness, fatigue, light-headedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

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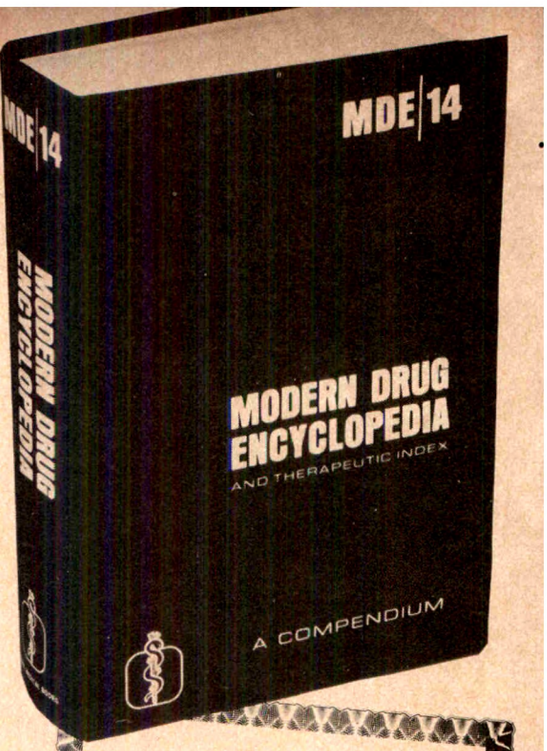

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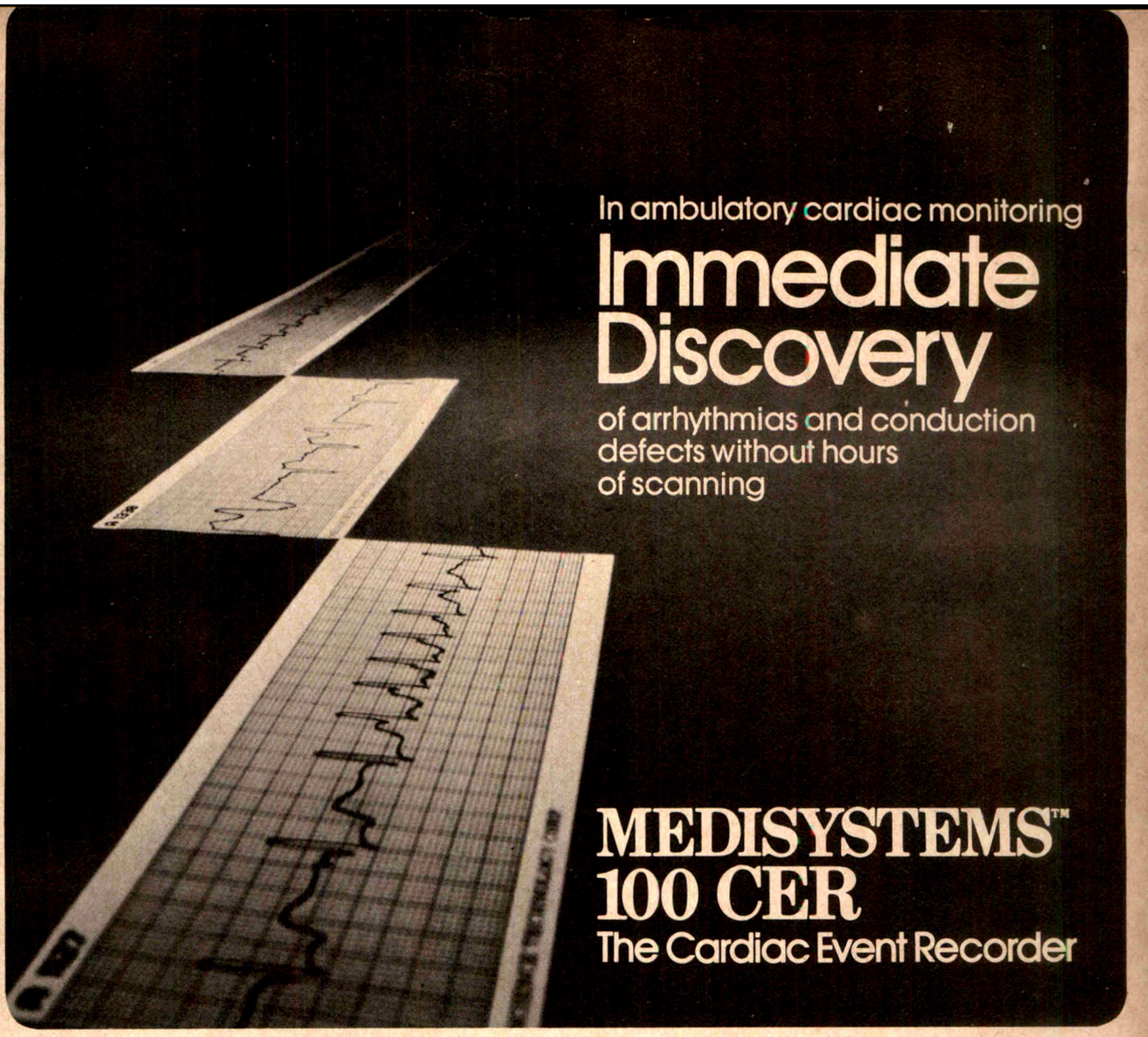

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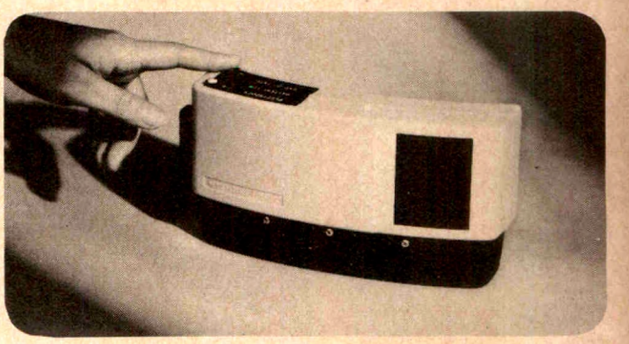

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Investigators have attributed the improvement to vasodilating effects of exercise, increased venous return and development of the collateral circulation. It is clear that exercise produces a tolerance for more exercise, and a program of regular walking, in the absence of any contraindications, appears to be an appropriate measure in the management of Peripheral Vascular Disease.

The Value of Proper Gait

Patients often compensate for claudication in calf muscles by adopting a shuffling gait. This "shuffling" utilizes calf muscles only minimally.

The diagram on this page illustrates the normal gait—described as "heel-and-toe" walking. Patients who are encouraged to become more conscious of their gait and to walk properly will utilize calf muscles to a greater degree—and maximize the therapeutic effects of a prescribed walking program.

The Role of Arlidin (nylidrin HCl)

Arlidin improves blood flow by dilating responsive vessels in skeletal muscles. The symptoms of ischemia may therefore be relieved thus encouraging the patient to begin or continue with an appropriate exercise program.

Furthermore, Arlidin maintains mean arterial pressure, thus maximizing delivery of blood to ischemic areas and minimizing the risk of postural hypotension. Its vasodilating effect in skeletal muscles and maintenance of mean arterial pressure make Arlidin an appropriate adjunct to other measures—such as walking—in the management of Peripheral Vascular Disease.*

PROPER HEEL-AND-TOE WALKING

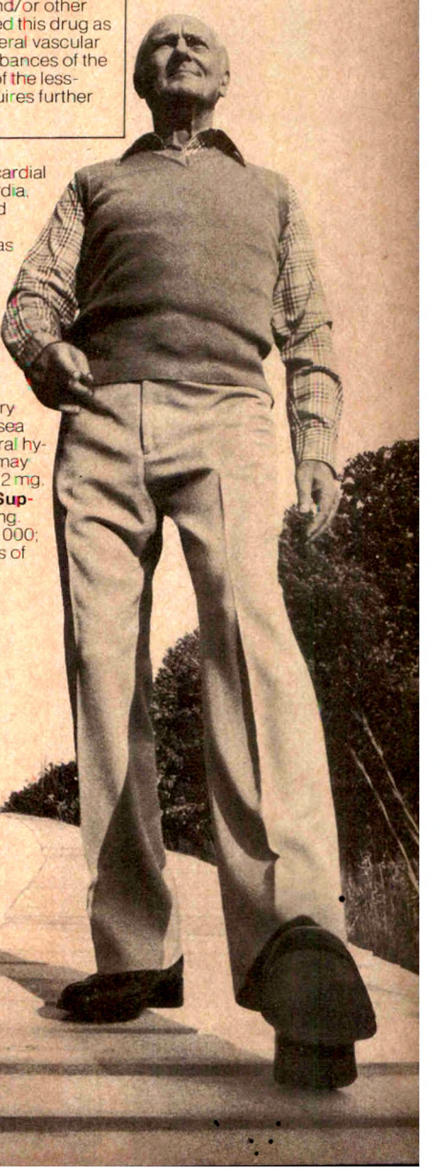
HEEL STRIKE PUSH-OFF HEEL STRIKE

You can obtain a more detailed version of this chart, explaining heel-and-toe walking to patients, from your USV Representative or by writing to Medical Department, USV Laboratories Inc., Tuckahoe, N.Y. 10707.

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).



The new prescription for Peripheral Vascular Disease

Walking & Arlidin® (nylidrin HCl)

†A bibliography of published papers on therapeutic walking is available upon request.

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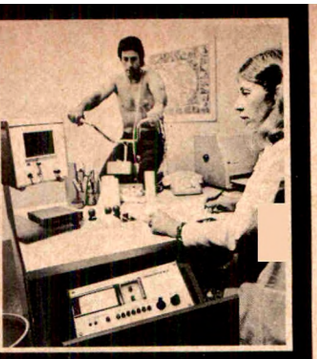

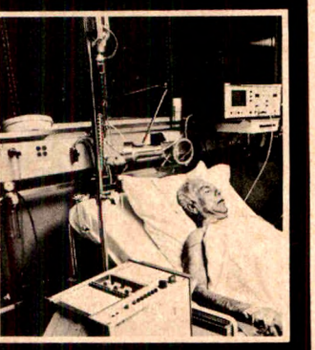

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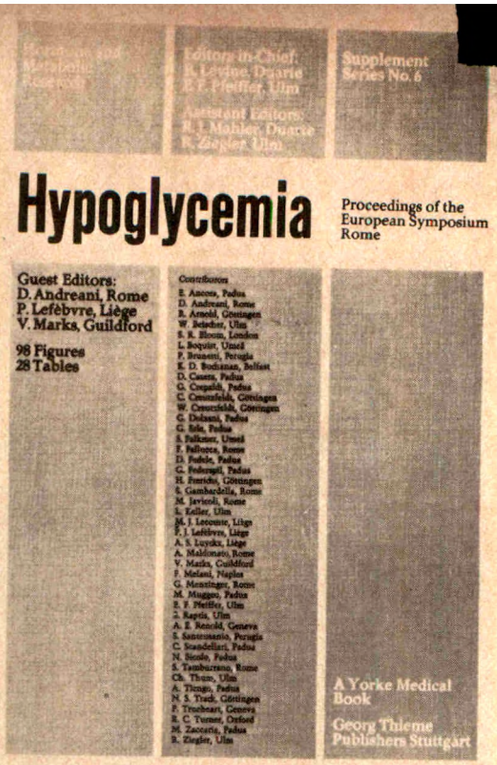

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This European (Rome) Symposium was the first free interchange of ideas among scientists in the various medical disciplines—physiology, internal medicine, endocrinology, clinical biochemistry, etc.—necessary to the understanding, diagnosis and treatment of hypoglycemia. The concentration was on the various aspects of insulin-producing tumors and the vexed question of essential reactive hypoglycemia. Special attention was given to the widespread misinterpretation of laboratory data relating to the prolonged oral glucose test which has resulted in the erroneous belief that "millions suffer from hypoglycemia."

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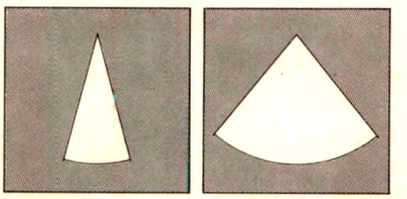

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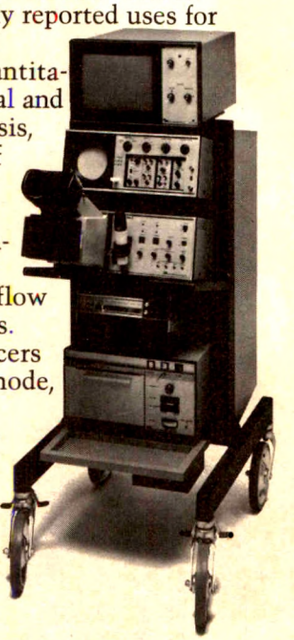

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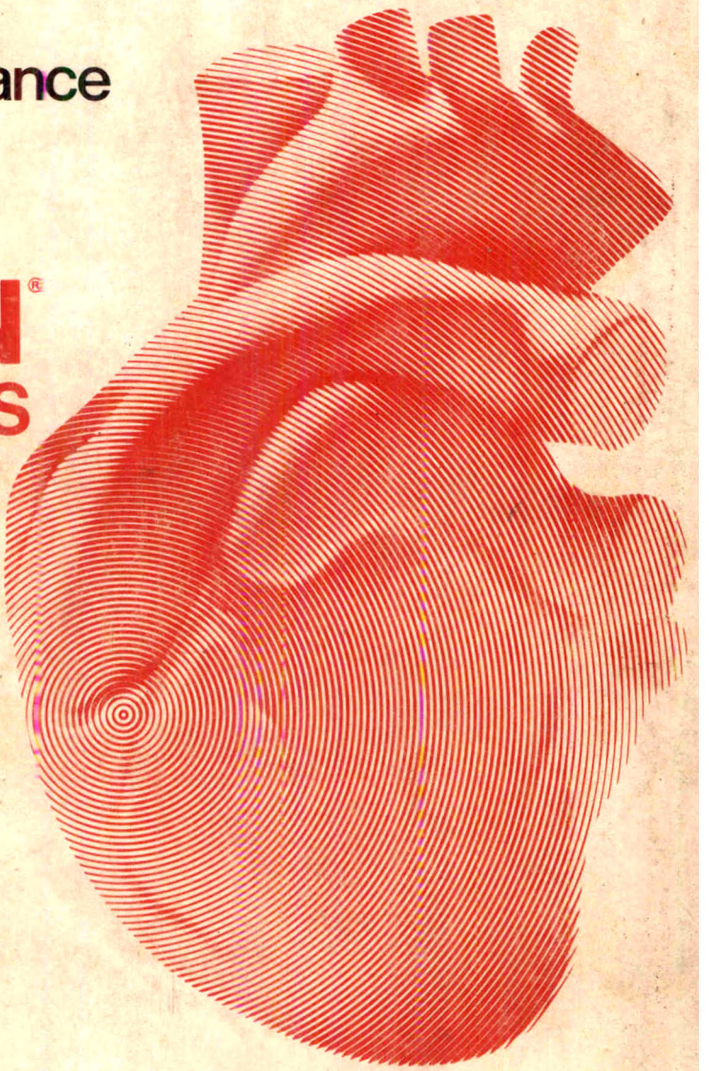

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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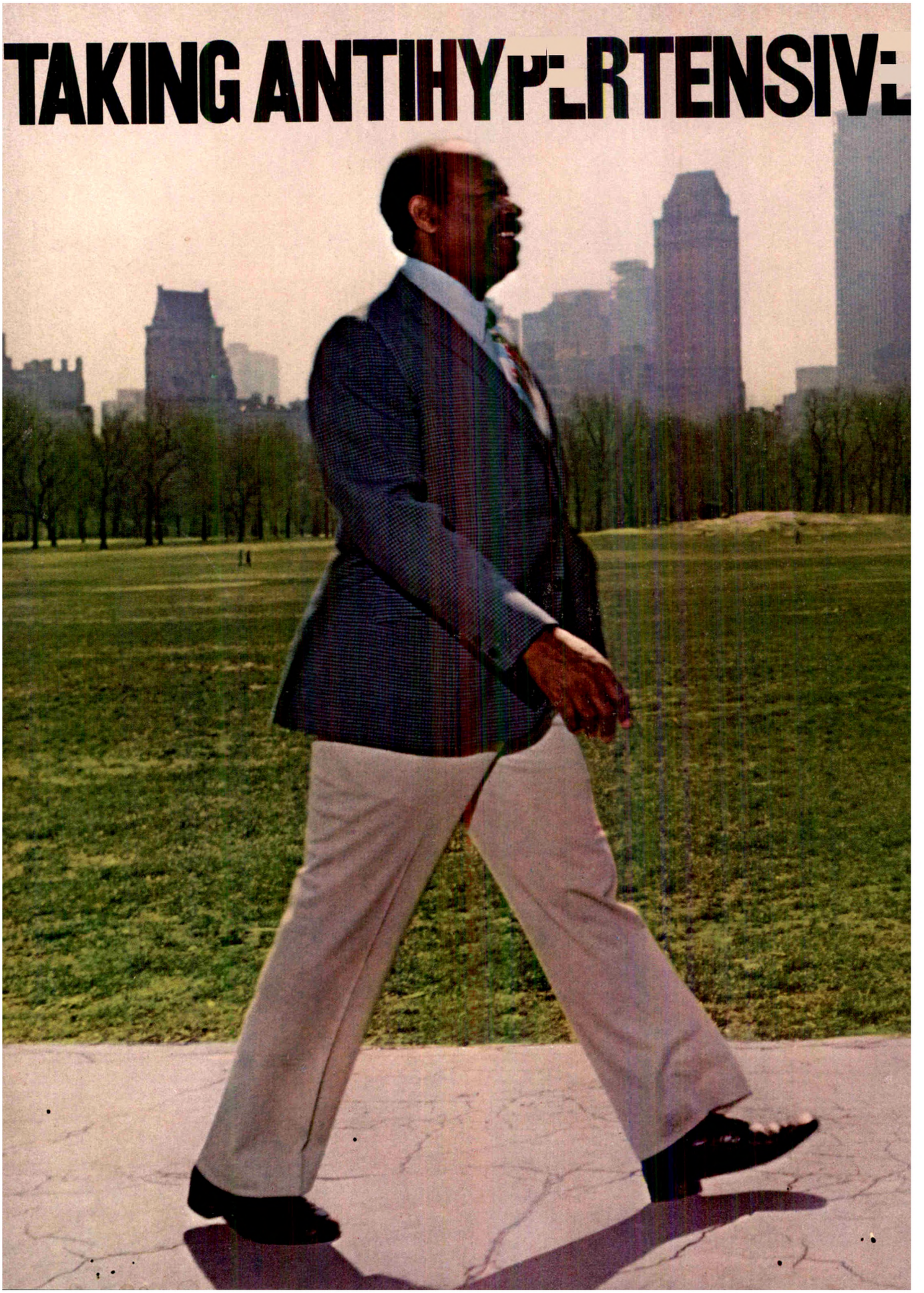

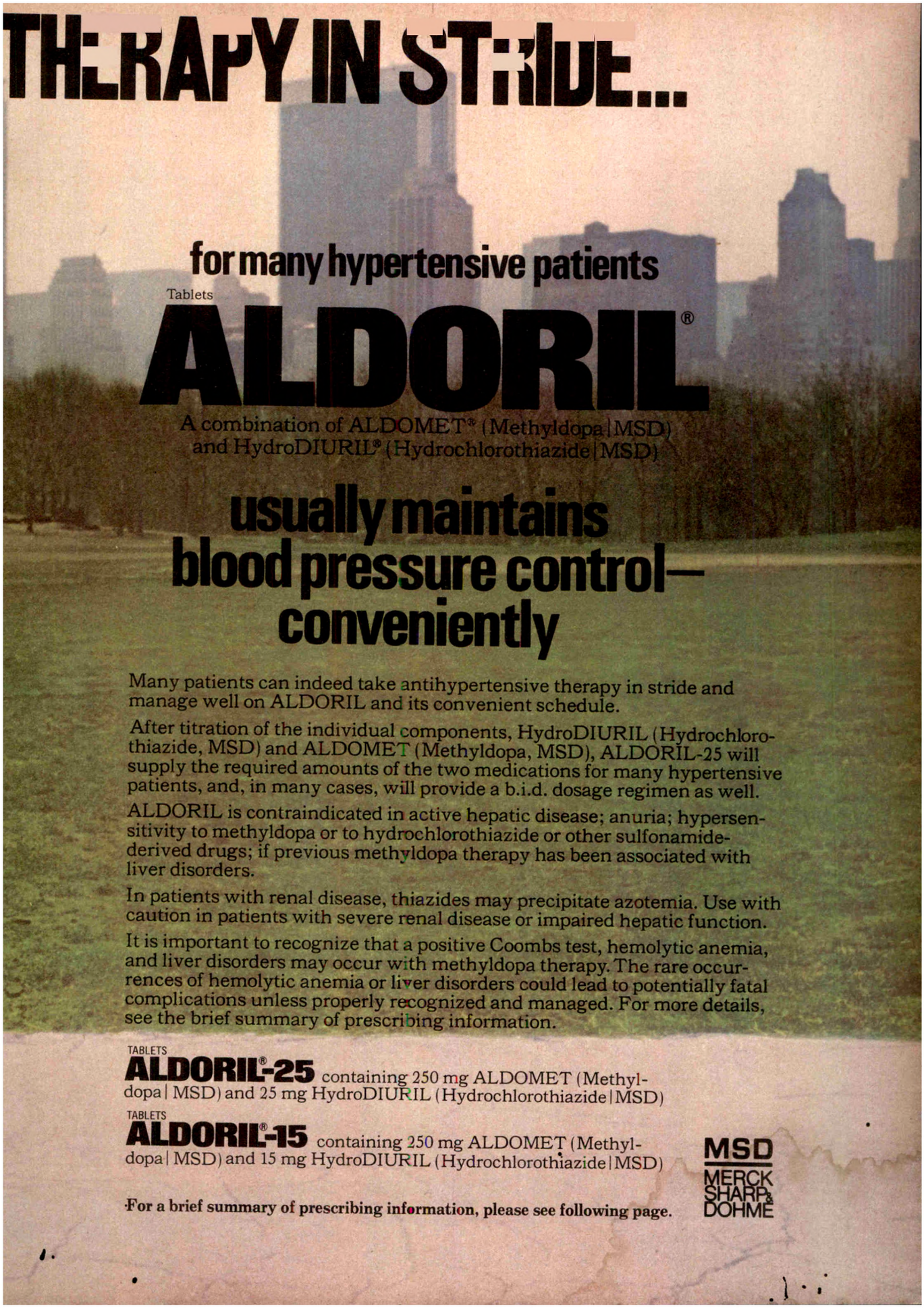
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In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.
It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.
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methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS
ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA— *Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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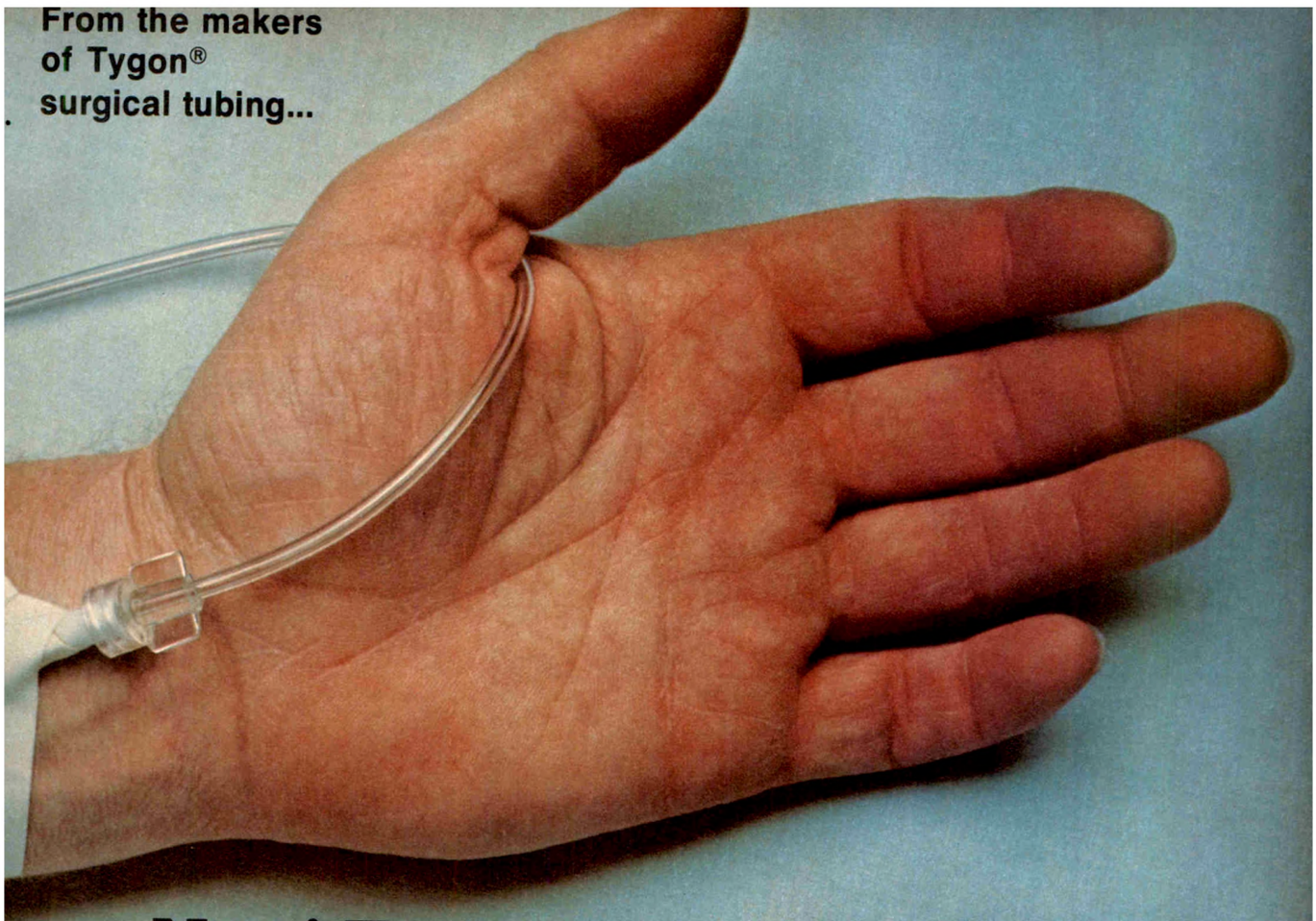

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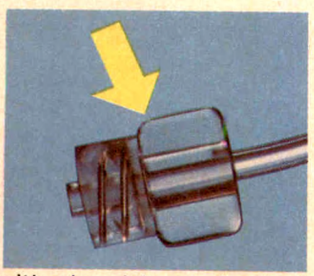

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Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing. 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

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623 **American College of Cardiology News**

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Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

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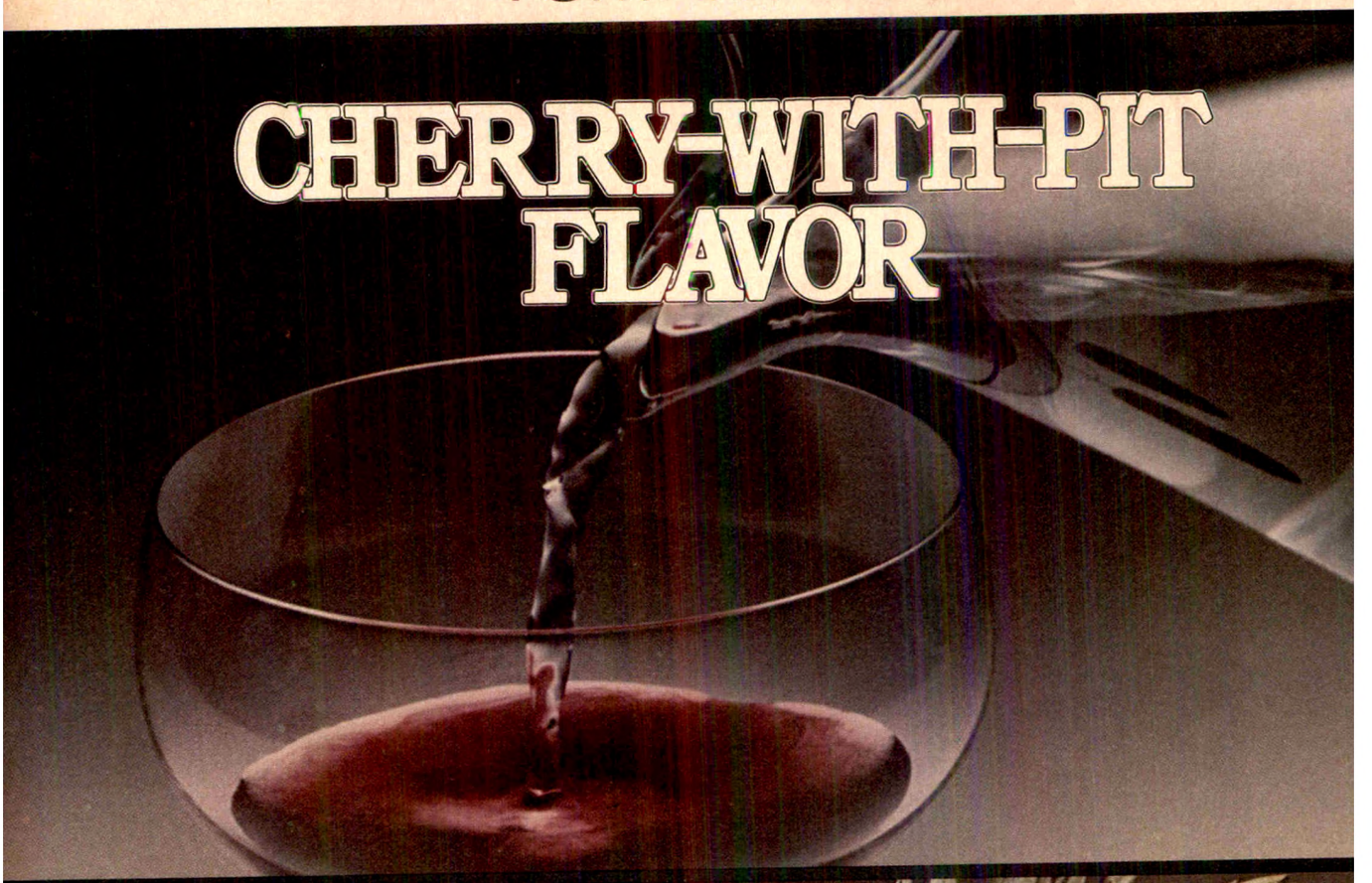

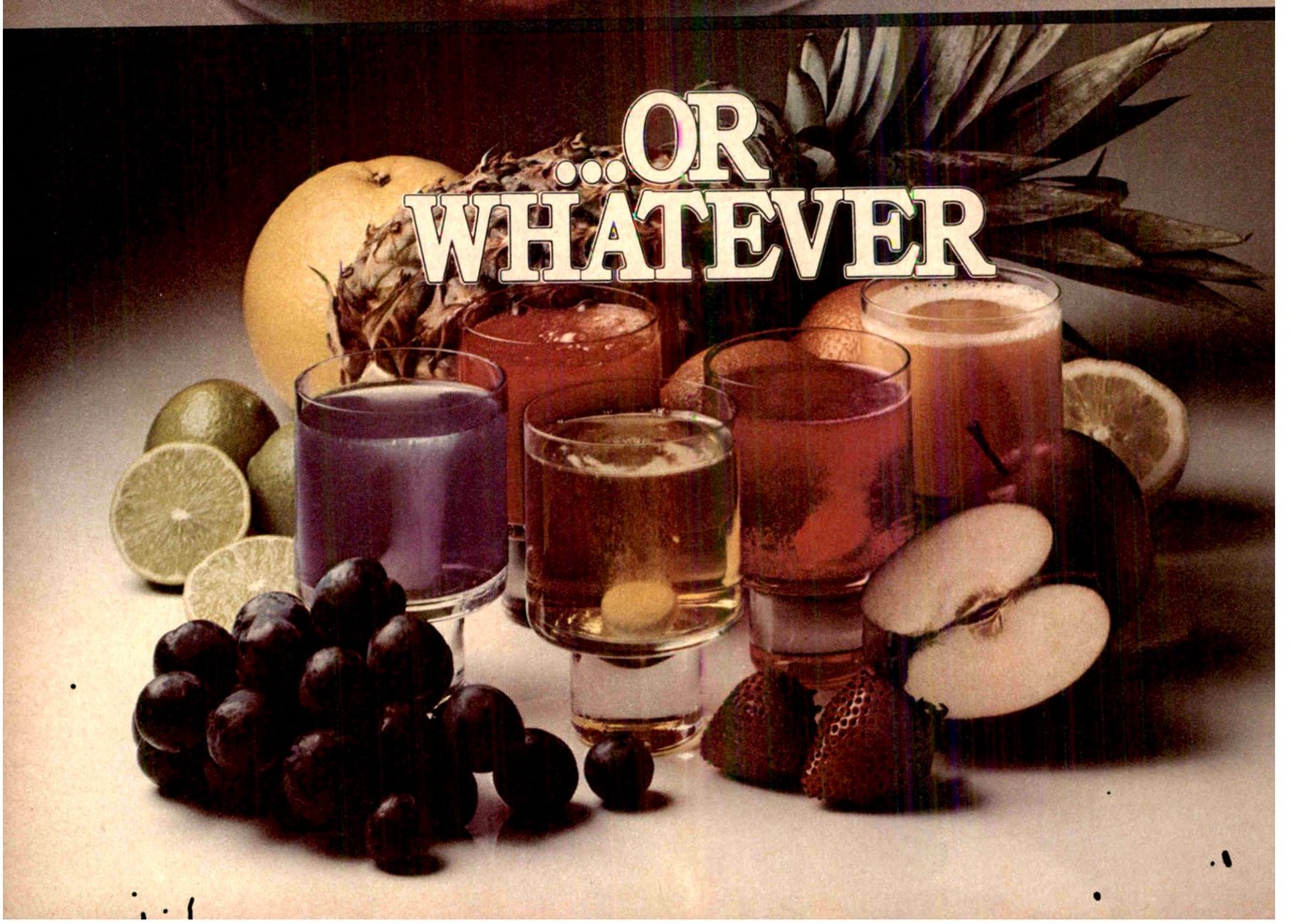

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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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MARCH 1978

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NUMBER 3

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CLINICAL STUDIES

469 Progressive Nature of Myocardial Injury in Selected Patients With Cardiogenic Shock

ALLEN L. GUTOVITZ, BURTON E. SOBEL and ROBERT ROBERTS

Data obtained in this study of 15 selected patients who manifested cardiogenic shock within 48 hours of admission, 5 with hypovolemic shock without myocardial infarction and 11 with myocardial infarction without shock, suggest that cardiogenic shock associated with initial infarction results from progressive myocardial damage underlying continuing release of MB creatine kinase into the circulation. In these patients cardiogenic shock reflects a vicious cycle of spreading myocardial injury, progressive compromise of cardiac function, exacerbation of ischemia and perpetuation of myocardial damage. In some patients who manifest shock with an initial infarction after admission to the hospital and who survive for at least 18 hours, interruption of progressive deterioration may be possible if favorable interventions can be implemented before a critical mass of myocardium has been destroyed.

476 Hemodynamics and Coronary Angiography in Idiopathic Hypertrophic Subaortic Stenosis

HECTOR LARDANI, JOSE A. SERRANO and RAMON J. VILLAMIL

One hundred eighteen patients with idiopathic hypertrophic subaortic stenosis were studied with cardiac catheterization and coronary arteriography to determine the incidence of coronary artery disease in such patients. There was a 25 percent incidence rate in subjects aged 40 years or older. Coronary artery disease was graded mild in seven, moderate in seven and severe (70 percent or more arterial stenosis) in nine patients. Seven of the nine patients with coexisting cardiomyopathy and severe coronary atherosclerosis had angina pectoris. The presence of idiopathic hypertrophic subaortic stenosis did not seem to influence the development of coronary atherosclerosis. One patient had an anomalous origin of the circumflex artery from the proximal segment of the right coronary artery. Patients with associated severe coronary atherosclerosis had a lower intraventricular pressure gradient at rest than the other patients.

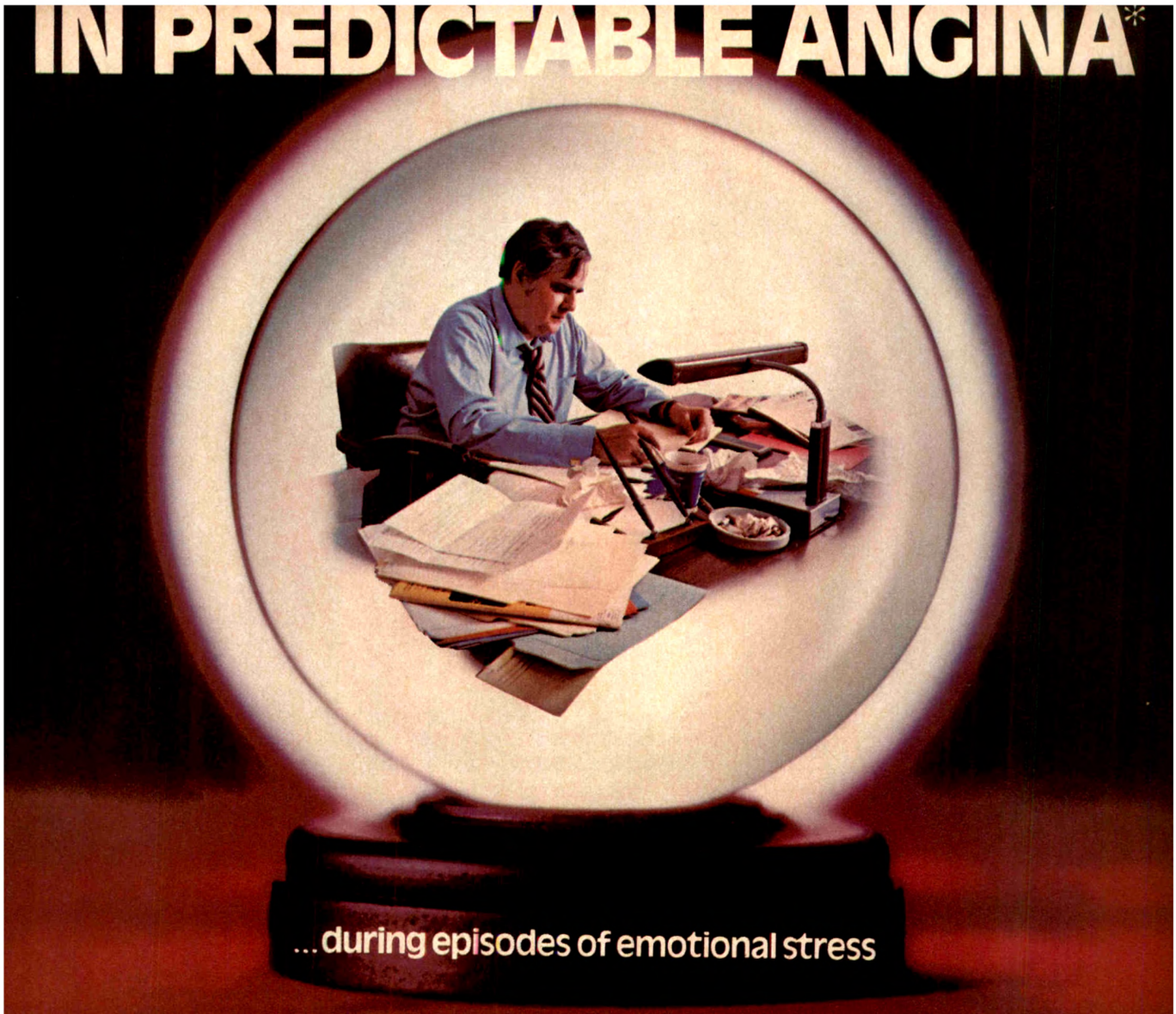
482 Anuloaortic Ectasia: Angiographic, Hemodynamic and Clinical Comparison With Aortic Valve Insufficiency

DAVID K. LEMON and CARL W. WHITE

Anuloaortic ectasia, a condition characterized by dilatation of the aortic ring and ascending aorta in patients without features of Marfan's syndrome or other known causes for aortic dilatation, represents an uncommon but serious cause of aortic insufficiency. In this study 35 patients with this condition were compared with 18 patients with isolated aortic valve insufficiency. The most common appearance of the aortic root enlargement was pear-shaped, but one third of the patients had symmetric diffuse enlargement and the remainder had only involvement of the sinuses of Valsalva. Dissection was a common complication, but neither the size nor the configuration of the aortic aneurysm was a reliable predictor of dissection. Despite surgical therapy, these patients do not have as good a prognosis as those with isolated aortic insufficiency.

Continued on page A14

IN PREDICTABLE ANGINA*



...during episodes of emotional stress

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

Onset of Effect: Two to five minutes.

Duration of Effect: One to two hours.

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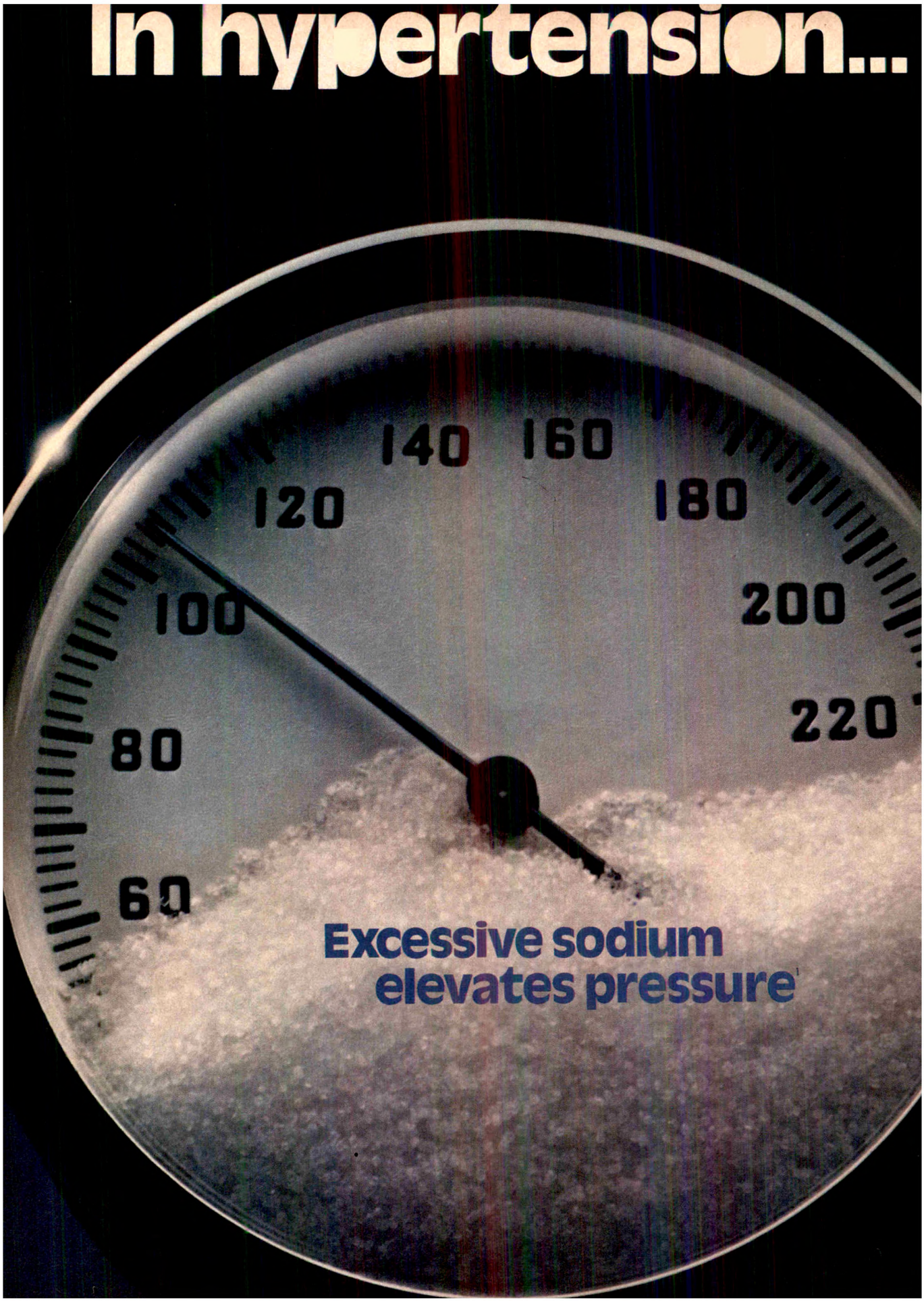

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As step-1 therapy

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As baseline diuretic in step-2 therapy

Reduced blood pressure resulting from the use of step-2 agents (reserpine, methyldopa, propranolol) may cause compensatory sodium retention, secondary volume expansion and, eventually, reelevation of blood pressure. For this reason, the National Task Force[2] recommends the use of diuretics as baseline agents with step-2 therapy. Hygroton is an "ideal" choice because of its sustained blockade of sodium retention, dosage simplicity and enhanced patient compliance.

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

References:

1. Laragh, J.H. et al.: Vasoconstriction - volume analysis for understanding and treating hypertension: The use of renin and aldosterone profiles, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, pp. 824-825. **2.** Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A Cooperative Study, JAMA 237:255, January 17, 1977.

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CONTENTS

487 Left Ventricular Performance in Patients With Atrial Septal Defect: Evaluation With Noninvasive Methods

KENNETH L. WANDERMAN, ILYA OVSYSHCHER and MOSCHE GUERON

Echocardiographic and systolic time interval studies in 18 patients with an atrial septal defect and in 45 patients whose defect had been repaired demonstrated that the mildly diminished overall left ventricular performance in atrial septal defect was related to the volume overload of the right ventricle and to the concomitantly diminished volume of the left ventricle rather than to any impairment of myocardial contractility. The size of the ventricle and its performance returned to normal after closure of the defect. Systolic time interval measurements in patients not operated on revealed a shorter mean left ventricular ejection time index, a longer mean preejection period index and a higher mean ratio of preejection period to ejection time. Systolic time intervals provide a measure of overall performance independent of any selective abnormality in motion of the left ventricular walls, and their use in conjunction with echocardiography is particularly suited to the study of atrial septal defect.

494 Value of the QRS Complex in Assessing Left Ventricular Ejection Fraction

JOSEPH ASKENAZI, ALFRED F. PARISI, PETER F. COHN, WILLIAM B. FREEDMAN and EUGENE BRAUNWALD

In this study of 73 patients with documented chronic coronary artery disease, the sum of R waves (ΣR), calculated (in mv) from six precordial and two augmented limb leads, correlated with both ejection fraction and augmented ejection fraction after a premature ventricular contraction. The best correlation occurred in patients with old anterior myocardial infarction and the poorest in those with old diaphragmatic myocardial infarction. A higher ΣR was associated with higher values for ejection fraction and augmented ejection fraction in patients with old myocardial infarction, a finding consistent with the experimental observations that viable myocardium is represented by epicardial R waves. Thus, the electrocardiogram may prove useful as a simple, readily available and noninvasive guide in the assessment of left ventricular function in patients with coronary artery disease.

500 Atrioventricular Block: Natural History After Permanent Ventricular Pacing

ARTHUR B. SIMON and ALAN E. ZLOTO

Sudden death was the most common mode of death in the 246 patients undergoing pacing for atrioventricular block between 1961 and 1974. Although preliminary data indicate that ventricular arrhythmias of a serious nature are common in these patients, so far there is little evidence that available antiarrhythmic agents decreased the frequency of complex ventricular arrhythmias consistently in this population, or that they decreased the incidence of late sudden death. Risk of death was greatest among patients with antecedent ischemic or hypertensive heart disease or congestive heart failure in the period before pacemaker implantation, patients older than 74 years at initial implantation and those receiving a pacemaker before 1965. Survival improved steadily over the period of study because of improvements in treating cardiovascular disease, including more effective treatment of congestive heart failure, greater availability of valve replacement for selected patients and elimination of immediate postoperative mortality.

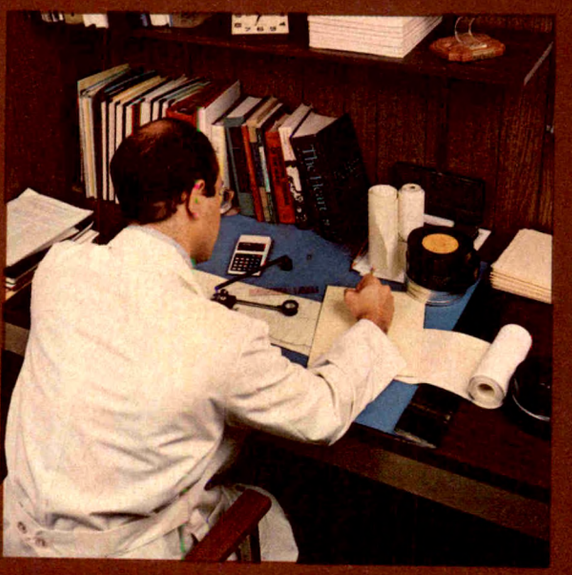
508 Thromboembolism in Mitral Porcine Valve Recipients

W. ALLAN EDMISTON, EARL C. HARRISON, GREGORY F. DUICK, WILLIAM PARNASSUS and FRANCIS Y. K. LAU

Despite anticoagulation therapy 5 of 22 single mitral porcine valve recipients (23 percent) had thromboembolic complications. Three had also had thromboembolic events before porcine heart valve implantation. Factors influencing thrombus formation such as left atrial enlargement, atrial fibrillation and a prosthetic device, present after porcine valve implantation, are indications for long-term anticoagulation therapy. In the autopsy patients thrombotic material seen on the valve cusps, at the tissue-valve interface and in the atrial chamber demonstrated that the underlying disease process, as well as the prosthetic mitral valve, continues to be a source of thromboembolic disease, even after mitral porcine valve implantation.

Continued on page A17

IF HE HAD THE E for M CATH LAB COMPUTER,



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512 Tissue Valve Replacement of Prosthetic Heart Valves for Thromboembolism

BRUCE A. REITZ, EDWARD B. STINSON, RANDALL B. GRIEPP and NORMAN E. SHUMWAY

These results indicate that rereplacement with a tissue prosthesis not only can be safely performed in patients with recurrent severe embolization after prosthetic heart valve replacement, but also significantly reduces the likelihood of additional embolic episodes. Patients with the first prosthetic valve had 0.65 embolus/year compared with 0.059 embolus/year after tissue valve replacement. The two primary indications for reoperation are (1) two or more episodes of thromboembolism despite satisfactory maintenance anticoagulation, and (2) evidence of prosthetic valve dysfunction due to obstructing thrombus. These results confirm the clinical usefulness of this procedure.

EXPERIMENTAL STUDIES

516 Central Neurochemical Factors Related to Serotonin Metabolism and Cardiac Ventricular Vulnerability for Repetitive Electrical Activity

STEPHEN H. RABINOWITZ and BERNARD LOWN

Sympathetic neural traffic to the heart can be diminished by administering serotonin precursors that localize in the central nervous system. A sustained increase of 50 percent in ventricular threshold resulted with the administration of biochemical agents (serotonin precursors) that presumably increased serotonin levels in the central nervous system of anesthetized dogs. This study demonstrates that such neuropharmacologic measures affecting central sympathetic activity may alter cardiac vulnerability and protect against ventricular fibrillation. It may be that pharmacologic treatments for prevention of sudden death should be focused on restraining the neurophysiologic triggers rather than protecting the cardiac target.

523 Experimental Myocardial Infarction. XVI. The Detection of Inotropic Contractile Reserve With Postextrasystolic Potentiation in Acutely Ischemic Canine Myocardium

WILLIAM E. BODEN, CHANG-SENG LIANG, CARL S. APSTEIN and WILLIAM B. HOOD, Jr.

Postextrasystolic potentiation after a single closely coupled extrasystole was systematically studied in eight open chest dogs to assess the progression of regional contraction abnormalities during a 10 minute occlusion of the left anterior descending coronary artery. The results showed that latent viability and contractile reserve may exist during brief periods of coronary occlusion. Such postextrasystolic potentiation produced marked inotropic augmentation, but not to control levels, for up to 10 minutes of ischemia. Despite a 50 percent decrease in border zone segment function, postextrasystolic potentiation consistently augmented mechanical performance to control levels throughout the ischemic period. These data suggest that early "pump failure" of the ischemic myocardium may be attributable to enhanced calcium ion influx produced by closely coupled extrasystoles, and that the mechanical performance of border zone ischemic myocardium can be augmented inotropically to control levels with postextrasystolic potentiation. Furthermore, wall motion abnormalities during brief periods of ischemia, such as seen in unstable angina, may be amenable to coronary revascularization.

METHODS

531 Variability in Sequential Measures of Left Ventricular Performance Assessed With Radionuclide Angiocardiography

ROBERT C. MARSHALL, HARVEY J. BERGER, LAWRENCE A. REDUTO, ALEXANDER GOTTSCHALK and BARRY L. ZARET

Three radionuclide studies separated by an average of 4.3 days performed in each of 20 patients show that such sequential quantitative radionuclide angiocardiography allows reproducible serial assessment of left ventricular performance with a low level of intrinsic variability. Variability in ejection rate was significantly greater in patients with normal function than in those with abnormal function. Regional wall motion analysis was constant in 19 patients. An interstudy difference of at least 5 percent is required for any change to be considered meaningful. The noninvasive and physiologic nature of this technique makes it ideally suited for study of the natural history of heart disease and the effects of medical and surgical intervention on left ventricular performance.

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CONTENTS

537 Measurement of Atrial Septal Defect During Cardiac Catheterization. Experimental and Clinical Results

TERRY D. KING, SANDRA L. THOMPSON and NOEL L. MILLS

As shown in this animal and patient study, a balloon catheter inflated with radiopaque dye can be used to measure accurately the size of experimental and clinical secundum atrial septal defects during cardiac catheterization. Persistent arrhythmias or other adverse effects of the procedure were not observed. These measurements aid in determining whether an ostium secundum defect is of the proper size and location to be closed transvenously and may be valuable in physiologic studies of atrial septal defects or other cardiac anomalies. Although the investigators still rely on the pulmonary to systemic flow ratio and left cineangiography for the first estimate of defect size, greater experience may permit balloon measurements to become a prime factor in determining the natural history and surgical significance of secundum atrial septal defects.

PEDIATRIC CARDIOLOGY

543 Echocardiographic Assessment of Left Ventricular Outflow Tract in d-Transposition of the Great Arteries

KALIM U. AZIZ, MILTON H. PAUL and ALEXANDER J. MUSTER

Echocardiographic assessment of the left ventricular outflow tract in 38 patients (aged 0.3 to 13 years) with complete d-transposition of the great arteries provided quantitative and qualitative data that were clinically useful in distinguishing between dynamic and fixed obstructive types of left ventricular outflow tract stenosis. Three groups could be determined on the basis of the left ventricular outflow tract/pulmonary arterial root ratio. Angiographically discrete or long segmental narrowing of the left ventricular outflow tract correlated well with the echocardiographic data. Echocardiographic measurements of left ventricular posterior wall thickness also correlated well with the severity of left ventricular outflow stenosis in these three groups.

552 His Bundle Electrogram After Intracardiac Repair of Tetralogy of Fallot. Analysis of Data in 59 Patients

THOMAS J. HOUGEN, MACDONALD DICK, II, MICHAEL D. FREED and JOHN F. KEANE

This study of His bundle electrograms in 59 patients after intracardiac repair of tetralogy of Fallot showed that a good hemodynamic result was associated with a normal H-V interval and a prolonged interval accompanied a poor result. These data also suggest the surgical technique during the intracardiac repair is related to the degree of injury to the specialized conduction system. A significant difference in the H-V interval between patients operated on before and after 1970 was not related to age at operation or hemodynamic result. The H-V interval is also generally normal in patients with few or no electrocardiographic abnormalities after intracardiac repair of tetralogy of Fallot and is generally prolonged in those with an electrocardiographic pattern of bifascicular or trifascicular block or transient complete heart block.

559 Wolff-Parkinson-White Syndrome in the Neonate

GRACE S. WOLFF, JOAK HAN and JOEL CURRAN

An electrocardiographic pattern consistent with Wolff-Parkinson-White conduction, type A was found in 8 of 16 infants who presented with paroxysmal supraventricular tachycardia in the neonatal period. Infants may have bypass pathways similar to or identical with a Kent pathway as part of normal maturation. The activity of these pathways is enhanced by the predominant cholinergic innervation of the neonatal heart. Resolution of the arrhythmias and the Wolff-Parkinson-White pattern occurs in most patients because of anatomic maturation of the conduction tissue, development of adrenergic innervation and a decrease in cholinergic dominance. All infants presenting with paroxysmal supraventricular tachycardia and Wolff-Parkinson-White syndrome should have long-term follow-up studies. The prognosis is favorable for the majority of pediatric patients with the Wolff-Parkinson-White syndrome who do not have coexisting structural heart disease.

Continued on page A20

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STUDIES IN HYPERTENSION

564 Hemodynamics of Postmyocardial Revascularization Hypertension

FETNAT M. FOUAD, F. GEORGE ESTAFANOUS and ROBERT C. TARAZI

Postmyocardial revascularization hypertension (173/101 mm Hg ± 5.9/2.4) developed in 10 of 17 subjects during a follow-up period of 4 to 6 hours after coronary bypass operation. These patients had a significant increase in total peripheral resistance and no significant change in cardiac index or heart rate. The mean rate of left ventricular ejection was not reduced by the increase in pressure and even tended to increase further in all but one patient. These results clearly demonstrate that the increase in blood pressure after coronary bypass surgery is related to an increase in total peripheral resistance arising from a generalized hemodynamic disturbance rather than a simple increase in cardiac output. Although circulating blood volume was not measured directly, the data do not suggest that the increase in arterial pressure after coronary surgery is related to hypervolemia induced by overtransfusion. This study indicates that better control of these hypertensive episodes can be obtained by a reduction in alpha sympathetic activity rather than a reduction of cardiac output with beta adrenergic blockade.

570 Alpha and Beta Adrenergic Blockade With Orally Administered Labetalol in Hypertension. Studies on Blood Volume, Plasma Renin and Aldosterone and Catecholamine Excretion

PETER WEIDMANN, RUDOLF DE CHÂTEL, WALTER H. ZIEGLER, JOSEF FLAMMER and FRANÇOIS REUBI

Significant changes in patients with benign essential hypertension treated for 6 weeks with the alpha and beta adrenoceptor blocking agent labetalol included a transient decrease in supine blood pressure reaching a maximum of 11 percent, persistent reduction in upright blood pressure, pulse rate (20 percent) and plasma renin activity (40 percent). Greater blood pressure reduction was achieved after adding chlorthalidone for combined therapy. Labetalol's antihypertensive action appears to be renin-independent and associated with a marked increase in free peripheral epinephrine. Side effects were often transient and mild, never necessitating discontinuation of drug therapy. The occurrence of orthostatic dizziness appeared to be dose-dependent.

REPORTS ON THERAPY

577 Orally Administered Prajmalium Bitartrate in Acute and Chronic Ventricular Arrhythmias

WULF-DIRK BUSSMANN, ERWIN MÜLLER, HANS-JÜRGEN HÄNEL and MARTIN KALTENBACH

Orally administered prajmalium bitartrate (20 mg every 6 hours) decreased premature ventricular contractions significantly in 19 patients. The full drug effect was attained after 6 hours, and after 12 hours the number of premature ventricular complexes averaged 30 percent of the initial value. In a second group of 14 patients, each treated with prajmalium bitartrate and also with procainamide, no significant differences were found in the antiarrhythmic action of the two drugs. This drug also proved effective in significantly reducing the rate of premature ventricular complexes to a mean of 4 percent of the initial value in nine patients with acute myocardial infarction. No side effects during short-term administration were observed.

584 Coronary Revascularization Under Age 40 Years: Risk Factors and Results of Surgery

HILLEL LAKS, GEORGE C. KAISER, HENDRICK B. BARNER, JOHN E. CODD and VALLEE I. WILLMAN

This study of 77 patients under the age of 40 undergoing coronary revascularization showed no operative deaths, a perioperative myocardial infarction incidence rate of 4 percent, a late myocardial infarction rate of 8 percent and a late mortality rate of 4 percent. In this group 71 percent returned to work; 29 percent remained unemployed. Despite the wide prevalence of predisposing factors, the prognosis and graft patency rate of these patients are similar to those of other groups. Coronary revascularization has a special application for these young patients because of the importance of employment and their ability to lead a vigorous life, which this surgical procedure can enhance.

Continued on page A22

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CONTENTS

590 **Management of Hypercholesterolemia: Evaluation of Practical Clinical Approaches in Healthy Young Adults**

RUSSELL V. LUEPKER, L. KENT SMITH, SARAH S. ROTHCHILD, ALBERT GILLIS, LEON KOCHMAN and J. RICHARD WARBASSE

Designed to determine how a sizable healthy working population with hypercholesterolemia can be most effectively identified and treated, this study found 146 hypercholesterolemic subjects aged 20 to 50 years among 6,000 employees at a worksite-located clinic at the Social Security Administration headquarters in Baltimore. At the end of 24 weeks, all intervention groups showed significant decreases ranging from 12 to 17 percent in serum cholesterol from the initial mean cholesterol level of 294 mg/100 ml; the control group had only a 4 percent decrease in cholesterol. The decreases in cholesterol correlated with weight loss and decrease in fasting serum triglycerides but not with the use of clofibrate. Change in cholesterol was not related to age, sex or lipid type (IIa or IIb). This study demonstrates that most type II hyperlipoproteinemic subjects in a working population can be identified and effectively treated by a lipid clinic or by private physicians.

DIAGNOSTIC SHELF

597 **Echocardiographic Features of Total Anomalous Pulmonary Venous Connection to the Coronary Sinus**

GARTH S. ORSMOND, HERBERT D. RUTTENBERG, F. BLANTON BESSINGER and JAMES H. MOLLER

Describing the echocardiographic features of six infants with total or near total anomalous pulmonary venous connection to the coronary sinus proves the usefulness of single crystal echocardiography in identifying the likelihood of this condition. An echo-free space measuring 7 to 9 mm behind the posterior left atrial wall in five infants was considered to represent the common pulmonary veins formed by the confluence of the anomalously connected pulmonary veins. A highly mobile linear echo with a double wave form per cardiac cycle recorded behind the posterior aortic wall and anterior mitral leaflet echoes was attributed to the anterior wall of the coronary sinus.

CASE REPORTS

602 **Elective Mapping and Surgical Division of the Bundle of Kent in a Patient With Ebstein's Anomaly Who Required Tricuspid Valve Replacement**

JOHN D. KUGLER, PAUL C. GILLETTE, DESMOND F. DUFF, DENTON A. COOLEY and DAN G. McNAMARA

On the basis of their experience with a 14 year old girl with Ebstein's anomaly and Wolff-Parkinson-White syndrome without supraventricular tachycardia, these surgeons recommend elective surgical division of the anomalous bundle in patients with this syndrome and heart disease requiring intracardiac repair even in the absence of preoperative tachycardias. After closure of an atrial septal defect and tricuspid valve commissurotomy, a recurrent debilitating paroxysmal supraventricular tachycardia required successful tricuspid valve replacement with concomitant cardiac mapping and division of the bundle of Kent. Postoperatively the patient had no more supraventricular tachycardias and could return to school. Her surface electrocardiogram showed no evidence of the Wolff-Parkinson-White pattern.

EDUCATION UPDATE

606 **Adult Cardiovascular Training Programs in the United States. American College of Cardiology**

Continued on page A24

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Anomalous Left Coronary Artery—G. G. Cayler and D. A. Cooley

History of Cardiac Pacing—I and II—P. P. Tarjan and V. Parsonnet

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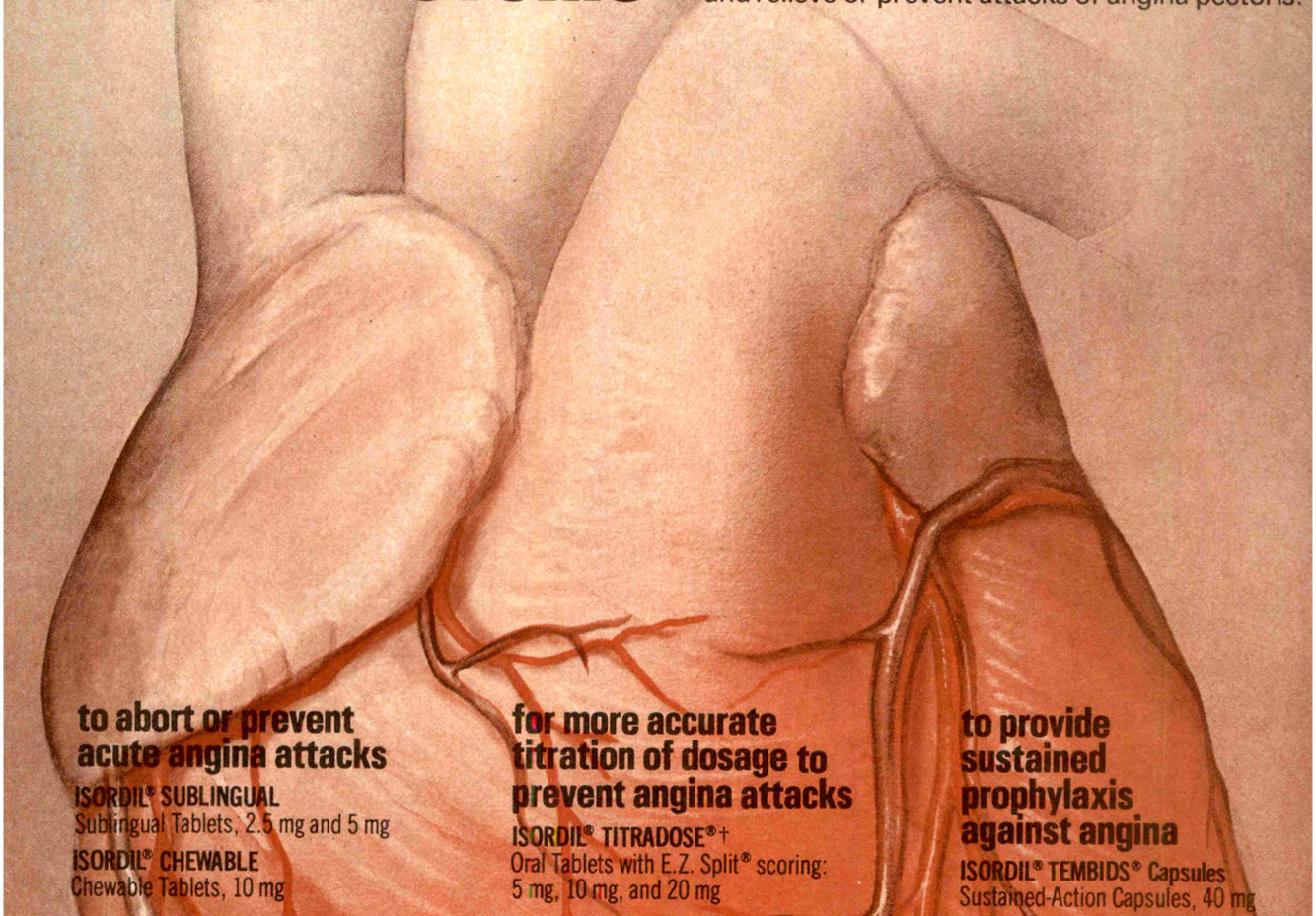
HELPS THE HEART IN THE CONTROL OF ANGINA PECTORIS*

The established use of Isordil in the management of angina pectoris for more than two decades has often been ascribed only to the vasodilatation it produces in the coronary arteries. Recent investigations, however, suggest that an even more important effect of this agent is to dilate peripheral arteries and veins. Arterial dilatation lowers impedance to left ventricular ejection, reducing afterload. Venous dilatation leads to venous pooling and a fall in right and left ventricular filling pressure, thus reducing preload.

With afterload and preload reduced, the amount of energy expended and oxygen consumed by the heart should be decreased. Isordil can thus reduce myocardial oxygen requirements and relieve or prevent attacks of angina pectoris.



to abort or prevent acute angina attacks

ISORDIL® SUBLINGUAL
Sublingual Tablets, 2.5 mg and 5 mg

ISORDIL® CHEWABLE
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for more accurate titration of dosage to prevent angina attacks

ISORDIL® TITRADOSE®†
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to provide sustained prophylaxis against angina

ISORDIL® TEMBIDS® Capsules
Sustained-Action Capsules, 40 mg

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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For Myocardial Perfusion Imaging

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used as an adjunct in the diagnosis
of coronary artery disease
or myocardial infarction

NEN New England Nuclear®

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or Diagnostic Use

November 1977

ıdications and Usage: Thallous Chloride Tl 201 may be useful myocardial perfusion imaging for the diagnosis and localiza- ɔn of myocardial infarction.

may also be useful in conjunction with exercise stress testing an adjunct in the diagnosis of ischemic heart disease (athero- lerotic coronary artery disease).

ontraindications: None known.

/arnings: In studying patients in whom myocardial infarction ischemia is known or suspected, care should be taken to sure continuous clinical monitoring and treatment in accor- ınce with safe, accepted procedure. Exercise stress testing ıould be performed only under the supervision of a qualified ıysician and in a laboratory equipped with appropriate resus- tation and support apparatus.

leally, examinations using radiopharmaceutical drug products especially those elective in nature—of women of childbear- g capability should be performed during the first ten days llowing the onset of menses.

recautions: Data are not available concerning the effect of arked alterations in blood glucose, insulin, or pH (such as is und in diabetes mellitus) on the quality of thallium Tl 201 ans. Attention is directed to the fact that thallium is a potas- ım analog, and since the transport of potassium is affected these factors, the possibility exists that the thallium may ewise be affected.

ıallous Chloride Tl 201, as all radioactive materials, must be ndled with care and used with appropriate safety measures minimize external radiation exposure to clinical personnel. are should also be taken to minimize radiation exposure to tients in a manner consistent with proper patient management.

o long-term animal studies have been performed to evaluate rcinogenic potential.

dequate reproduction studies have not been performed in imals to determine whether this drug affects fertility in males females, has teratogenic potential, or has other adverse ects on the fetus. Thallous Chloride Tl 201 should be used in egnant women only when clearly needed.

is not known whether this drug is excreted in human milk. As general rule nursing should not be undertaken when a patient administered radioactive material.

fety and effectiveness in children have not been established.

lverse Reactions: Adverse reactions related to use of this ent have not been reported to date.

Dosage and Administration: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

How Supplied: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0, and 9.0 millicuries of Thallous Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

Catalog Number NRP-427

New England Nuclear
Radiopharmaceutical Division
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Call toll free: 800-225-1572
(In Massachusetts and International: 617-482-9595)

Canada: NEN Canada Ltd., 2453 46th Avenue, Lachine, Que. H8T 3C9, Telephone: 514-636-4971, Telex: 05-821808
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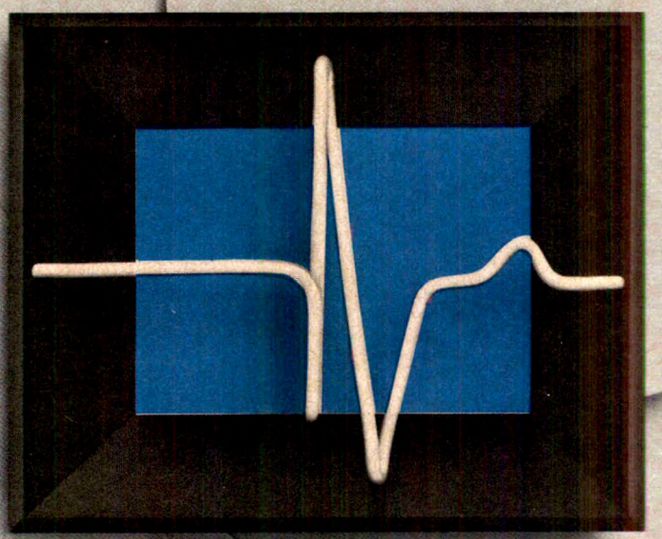

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Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate indicated for the relief of angina pectoris (pain associated v coronary artery disease). It is not intended to abort the acu anginal episode but it is widely regarded as useful in the pr phylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaeryth tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) a contraindicated in patients who have a history of sensitivity to drug.

Warning: Data supporting the use of Peritrate (pentaerythritol nitrate) during the early days of the acute phase of myocardia infarction (the period during which clinical and laboratory find are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who ha glaucoma. Tolerance to this drug, and cross-tolerance to othe nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been p dominantly related to rash (which requires discontinuation of cation) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In cases severe, persistent headaches may occur.

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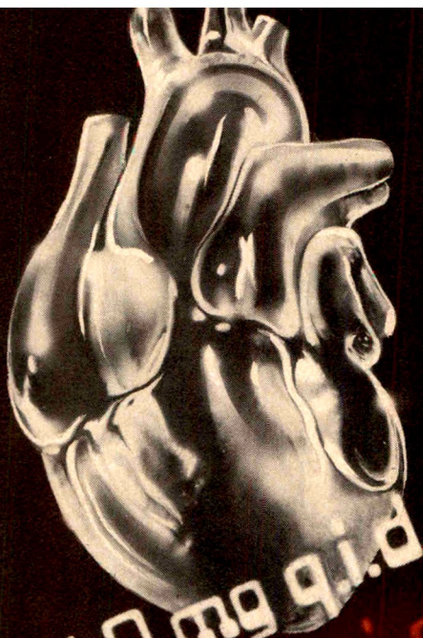

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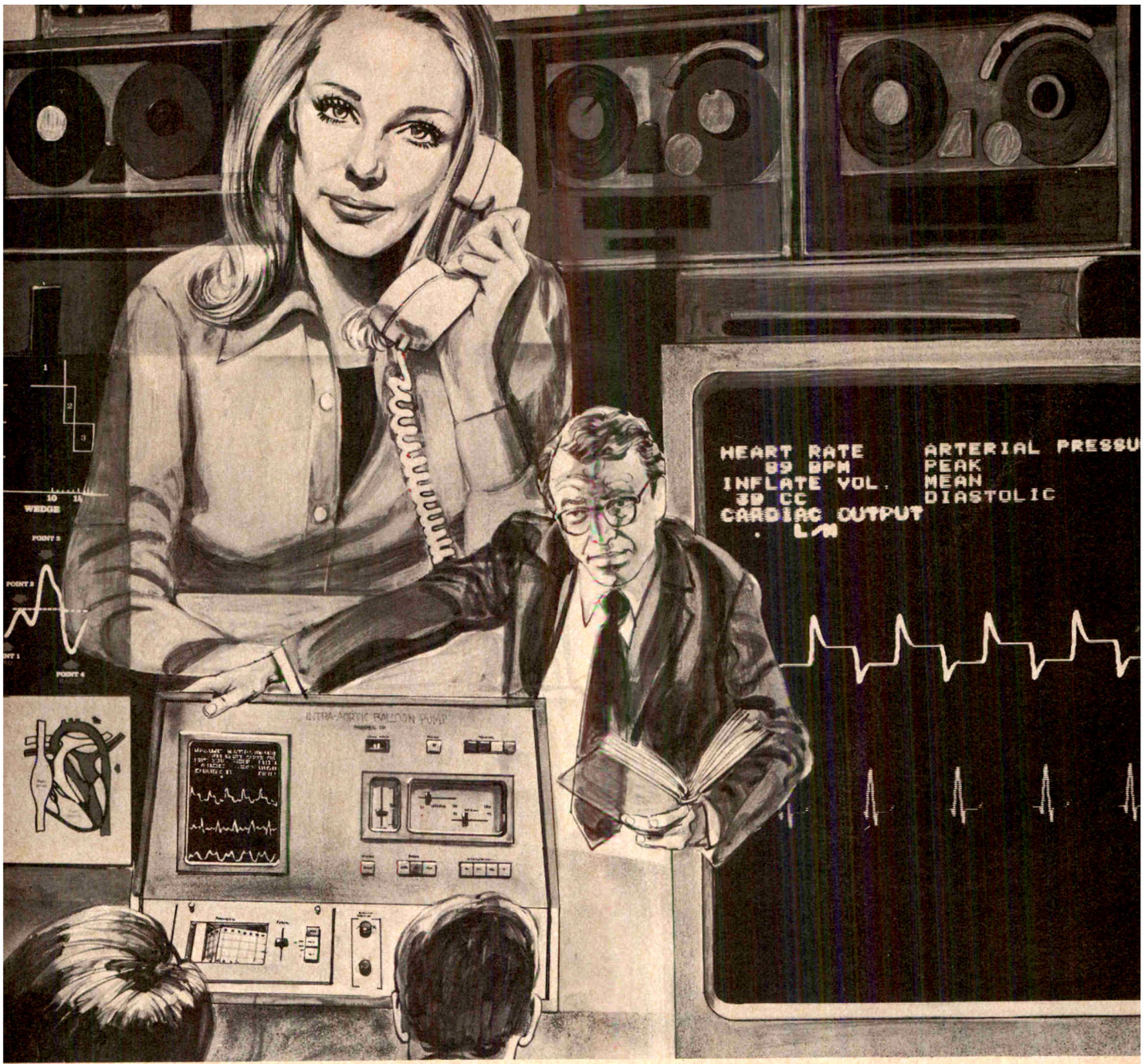

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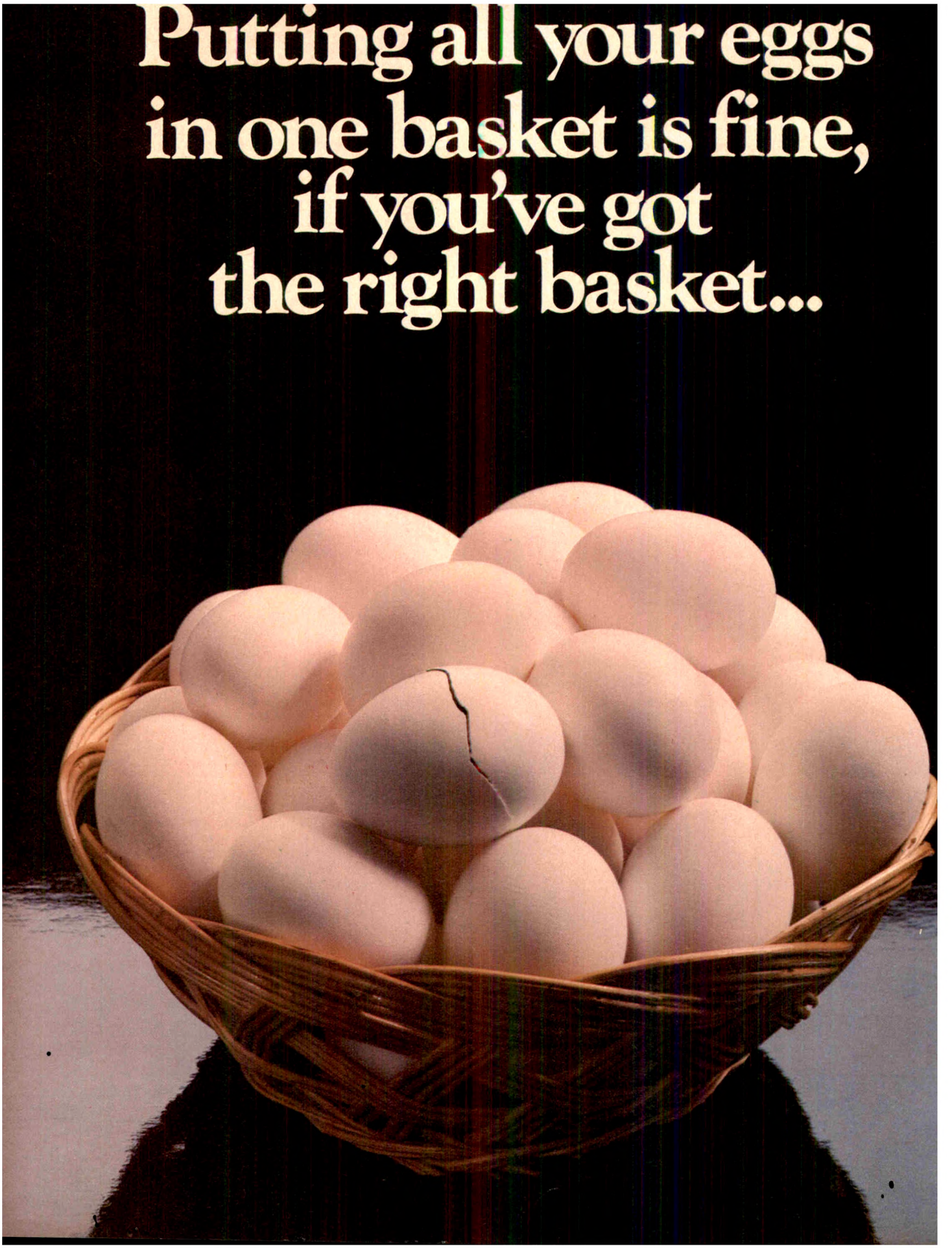
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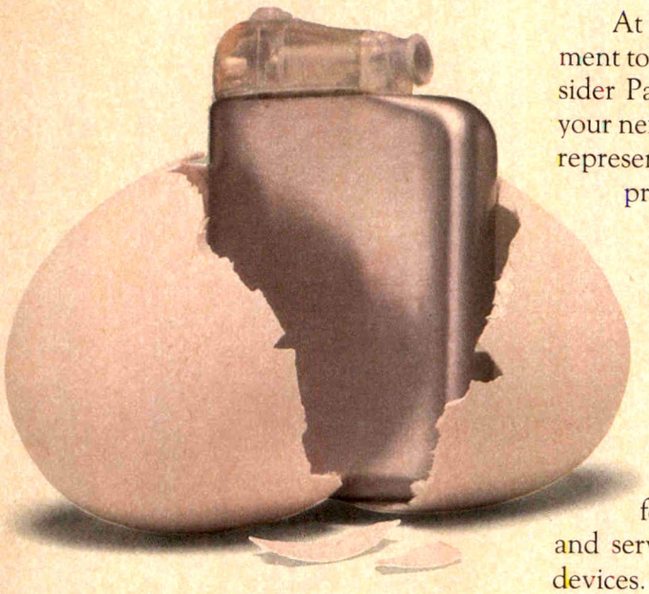

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- Catapres lowers blood pressure promptly.
- No contraindications.
- Some patients may have dry mouth, drowsiness, and sedation. Tell them that these tend to diminish with continued use.
- Giving the larger part of the divided dose at bedtime can help alleviate drowsiness and sedation.

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- Little impotence, depression or postural hypotension.
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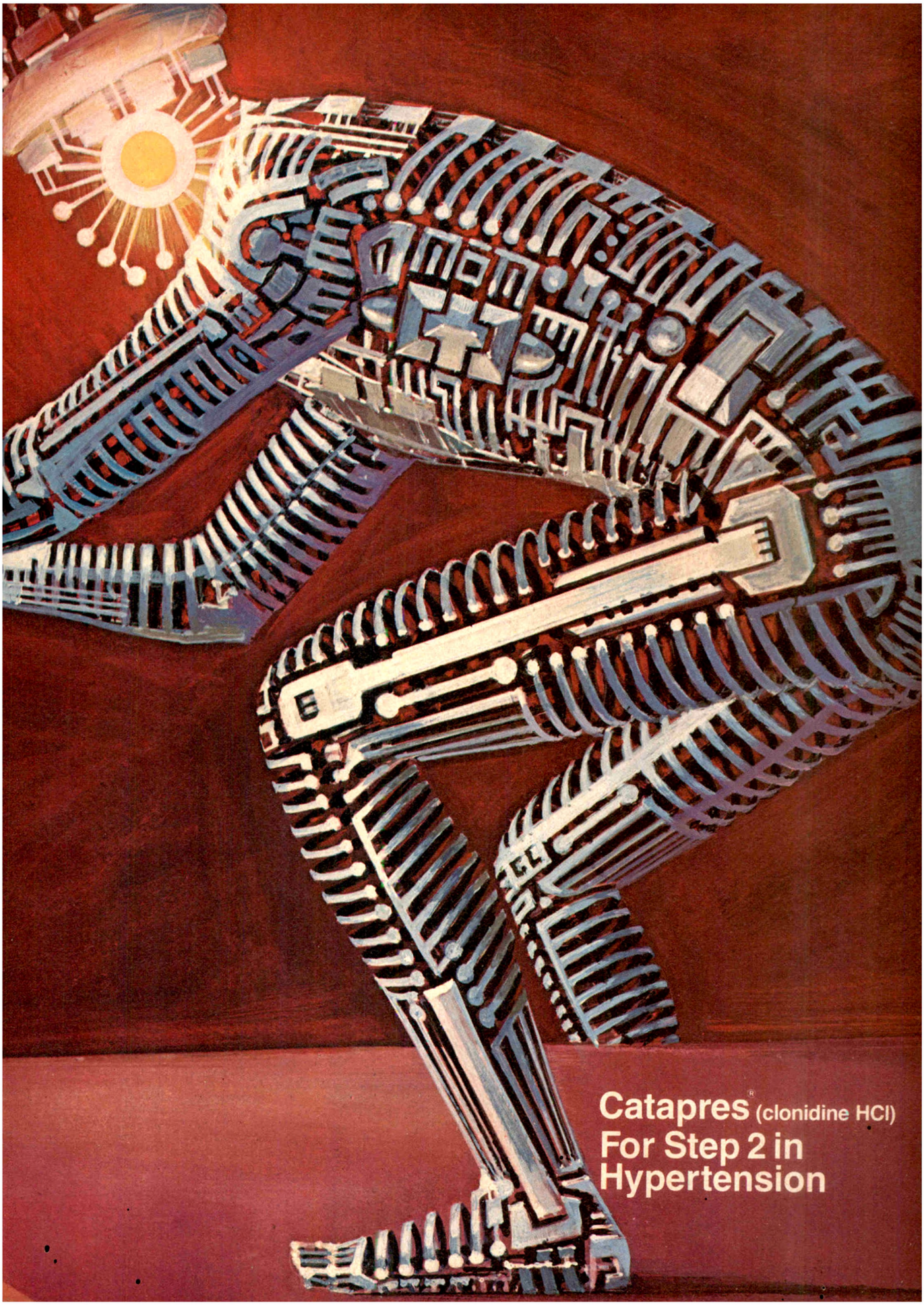
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(clonidine HCl)

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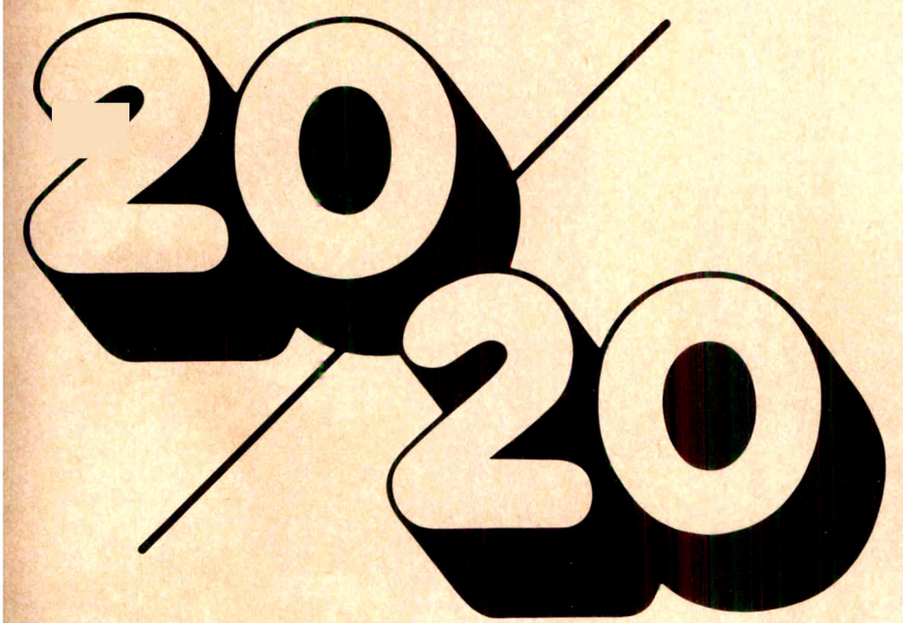

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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potenc It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetu *Usage in Children:* No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consultin their physician. Rare instances of hypertensive enceph lopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pres sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machiner or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any oth agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochlorid should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continue therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver func tion tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patien receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient eleva tion of blood glucose, or serum creatine phosphokinas congestive heart failure, Raynaud's phenomenon; vivi dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and ment depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of th eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somno lence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of a analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosag

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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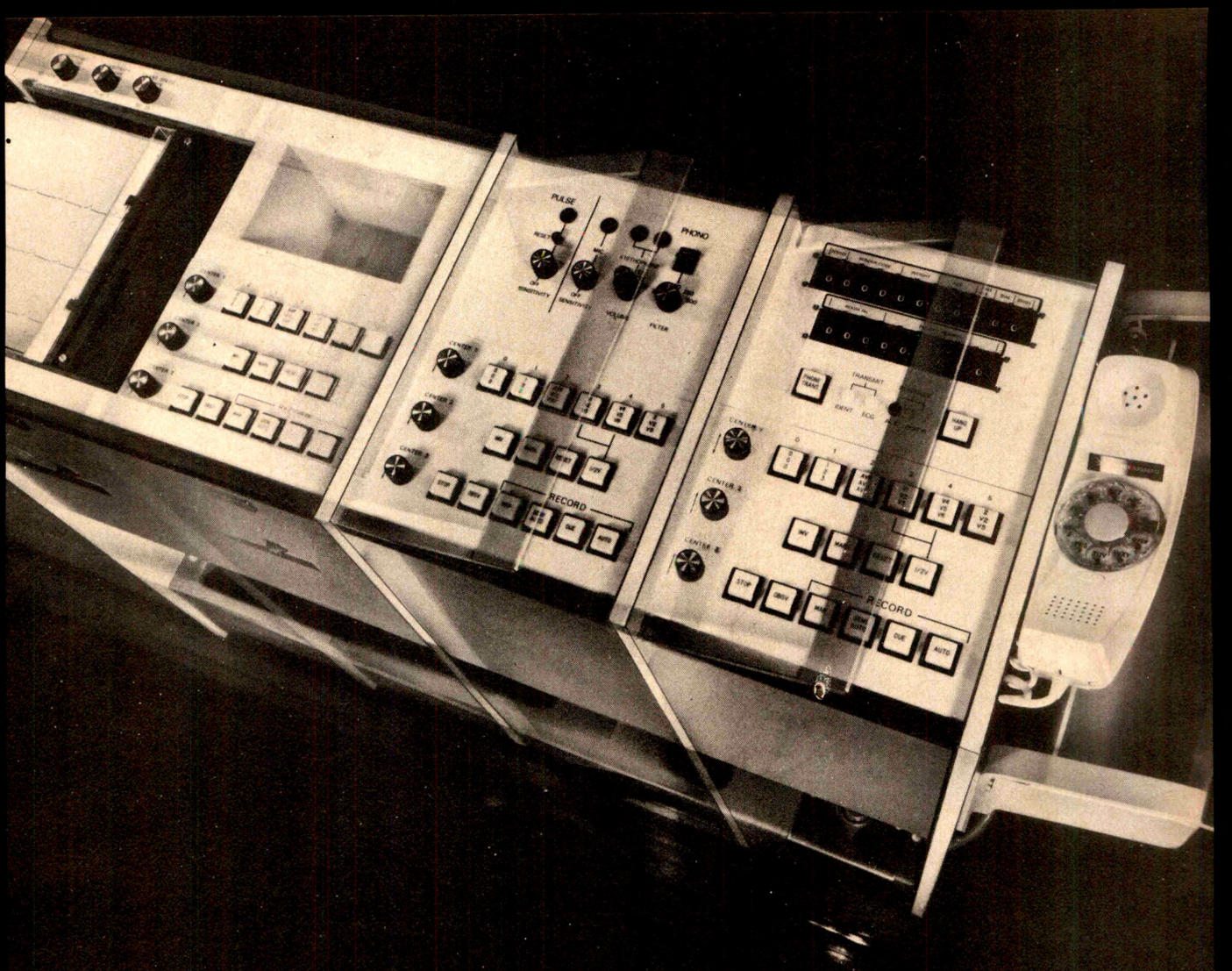

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THE INITIATION OF THE HEARTBEAT

DENIS NOBLE, University of Oxford. "A remarkably fine book and one that was badly needed.... I recommend this book without reservation to students of physiology and to serious students of medicine." —*The Quarterly Review of Biology*

1975 168 pp.; 70 illus. $13.95

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200 Madison Ave., New York, New York 10016

PRONESTYL® TABLETS (Procainamide Hydrochloride Tablets)
PRONESTYL® CAPSULES (Procainamide Hydrochloride Capsules U.S.P.)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as capsules and veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) and Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg. and 500 mg. tablets and capsules are also available in bottles of 1000.

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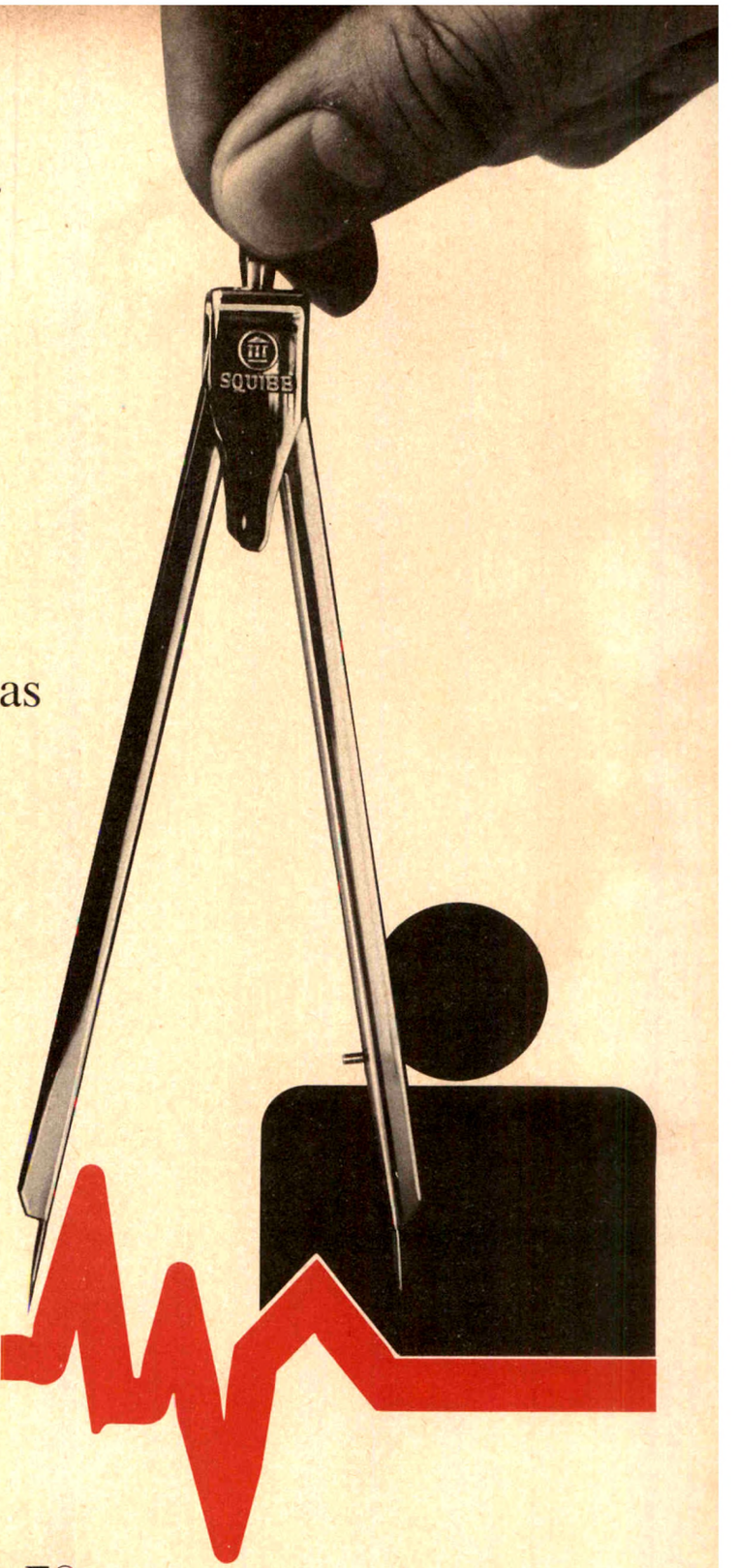
tried and true

in the treatment of life-threatening arrhythmias



Documented effectiveness in ventricular arrhythmias; indicated for certain atrial arrhythmias as well.

Backed by 26 years of clinical experience; over 15,000,000 prescriptions written!

Extensively used and studied in post-MI patients.

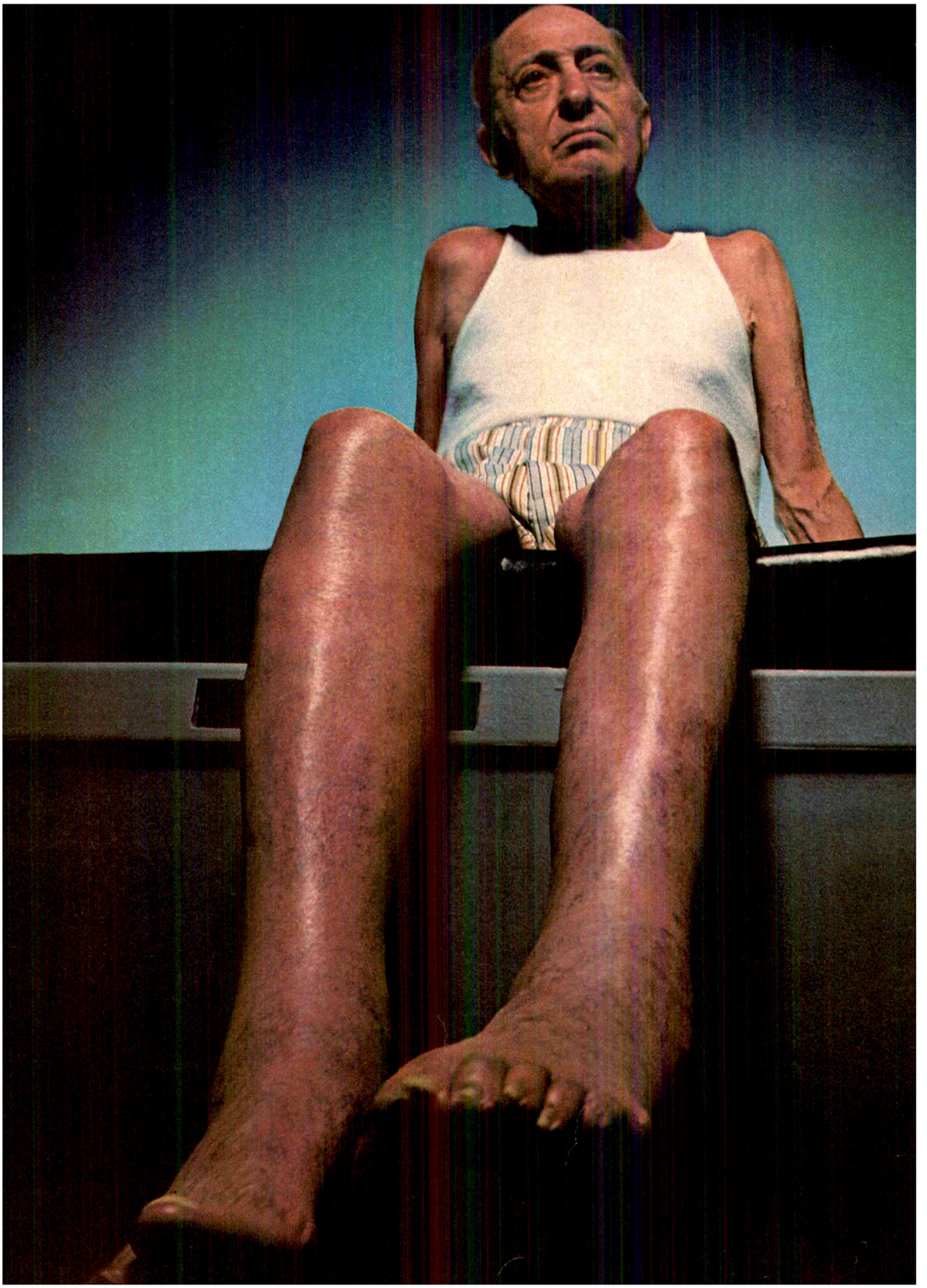
Compatibility with other cardiovascular drugs researched.

Three oral strengths (250mg, 375mg, 500mg) for dosing flexibility; available in easy-to-swallow veneer coated tablets.

See preceding page for brief summary.

Pronestyl® Tablets
Procainamide Hydrochloride Tablets

Trustworthy antiarrhythmic therapy



In cardiac edema...

the diuretic most likely to succeed.

It can outperform the thiazides in sodium loss

Lasix® (furosemide) has a greater potential for ridding the body of excess sodium and water than any other commonly used diuretic. A potential that has been realized in multiple comparative studies in patients with cardiac edema.

That's why Lasix is the diuretic most likely to succeed in all degrees of cardiac edema.

It need not go beyond them in potassium loss

With Lasix, the key to minimizing electrolyte disturbances is proper dosage. For if you control the cardiac patient's urine output and edema by titrating the dosage, the result likely will be excretion of less potassium because Lasix produces a dilute urine. As with any diuretic, electrolyte depletion can occur during therapy with furosemide. Careful clinical and laboratory observations are recommended.

And it often works where thiazides can't

Unlike other commonly used diuretics, Lasix can be useful in patients with severely depressed renal function. Even in the presence of renal insufficiency with acidosis, alkalosis or hypoalbuminemia, Lasix has been found both effective and well tolerated. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. Lasix is contraindicated in anuria.

The basic unit–
for initial therapy.
40 mg tablets.

The adjuster unit–
for maintenance therapy.
20 mg tablets.

LASIX® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide).

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs. Patients not adequately controlled with thiazides probably will not be adequately controlled with furosemide.

Contraindications: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. Continued use if increasing azotemia and oliguria occur during treatment of severe progressive renal disease. Hepatic coma. Electrolyte depletion. History of hypersensitivity to the compound.

Warnings: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Perform frequent serum electrolyte, CO_2 and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. **Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital.** Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions.

Precautions: As with any potent diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Since furosemide potentiates the effect of antihypertensive medications, reduce the dose of these agents when furosemide is administered to edematous hypertensive patients. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Cases of tinnitus and reversible hearing impairment have been reported when parenteral furosemide therapy preceded oral use. There are also reports of irreversible hearing impairment. Usually, ototoxicity has been reported when doses of furosemide exceeding several times the usual recommended dose were injected rapidly in patients with severe impairment of renal function who were also often receiving other drugs known to be ototoxic. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, it has been reported that an infusion rate not exceeding 4 mg furosemide per minute has been used.) Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Exercise great caution in administering curare or its derivatives to patients undergoing furosemide therapy, and it is advisable to discontinue furosemide for one week prior to any elective surgery.

Adverse Reactions: Various forms of dermatitis, urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea. Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis, which responded to treatment. Although relationship to the drug has not been established with certainty, the following rare adverse reactions have been reported: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli, and acute pancreatitis. Furosemide-induced diuresis may be accompanied by weakness, fatigue, light-headedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Q6689J-178

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InterLith™-RP.

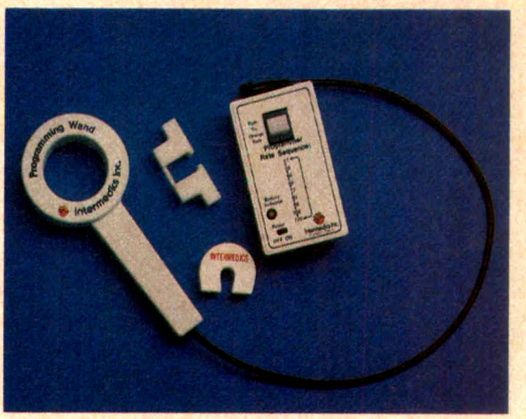
The pacemaker with a fail-safe rate programming design.

It took Intermedics to combine the most straightforward, uncomplicated rate programming system in the industry with the proven reliability of c-mos circuitry. Utilizing the superior longevity of a lithium power cell, Intermedics now offers you one of the smallest, lightest, most comfortable programmable pacemakers available...the InterLith-RP.

This pacemaker, unlike others on the market, utilizes circuitry that has been uniquely designed to avoid accidental reprogramming. This fail-safe feature requires the occurrence of two simultaneous electrical events; first, the magnetic reed switch must be closed and secondly, the programmer must be activated in immediate proximity to the pacemaker. The nine programmable rates are 51, 55, 60, 65, 72, 80, 90, 103 and 120 BPM. The rate is incremented from one value to the next by simply depressing the programming button.

A triumph of design, the InterLith-RP is hermetically sealed in tissue-compatible interference-resistant 316L stainless steel and measures only 6.0 cm × 4.6 cm × 1.5 cm (bipolar unit measures 6.3 cm in height), enabling a smaller incision resulting in a more cosmetic pocket. All edges are smoothly rounded for greatest patient comfort.

A lithium cell, plus low current drain under load, give the InterLith-RP a potential longevity in excess of 12 years*; like all other Intermedics pacemakers, the InterLith-RP is backed by a replacement credit agreement. Its universal connector readily accepts Intermedics' leads as well as most manufacturers' leads without adapters, making it an excellent choice when a replacement pulse generator is needed. InterLith-RP. The better programmable pacemaker.



For the location of your nearest Intermedics representative, or for additional information about our products, call toll-free 1-800-231-2330. In Texas, call collect 1-713-233-8611.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541

*Based on 72 BPM, 500 OHM load and 100% pacing.

InterLith is a trademark of Intermedics, Inc.

Note: The InterLith RP is currently being clinically evaluated.

Intermedics Pulse Generators

INDICATIONS FOR USE Pacemakers may be used in any application where asynchronous or demand ventricular pacing is indicated. These include congenital or acquired complete heart block which may be continuous or intermittent in nature, various types of sinus node dysfunction, WPW syndrome, carotid sinus hypersensitivity, drug induced bradycardia, and various ventricular arrhythmias.

The above list is not intended to be complete. The indications for pacing are increasing as the devices become more sophisticated and as methods for patient management become more widely understood.

PRECAUTIONS Implanted cardiac pacemakers have a finite service life and a relatively wide variability in service life. Factors affecting service life include the initial capacity of the battery and the shelf storage time of the manufactured pulse generator. Once implanted the anticipated service life of the generator is modified by variations in electrode system resistances, stimulation rate, and the percentage of time during which the pacemaker is inhibited. The current drain on the battery when inhibited is less than one-third of that when pacing with a typical lead installation. Other factors contributing to wide variability in service life are random electronic component failures.

All sensing pulse generators are inherently susceptible to magnetic electrical and electromagnetic fields. While design features are incorporated to minimize this susceptibility, an extraneous signal of sufficient strength and with characteristics which mimic normal cardiac activity can influence their operation. Additionally, certain environmental sources can couple sufficient energy into a cardiac pacemaker system to damage the pulse generator. Specifically, the implanting physician and the patient should be warned about the following:

(1) Electrocautery–Surgical use of electrocautery may cause temporary inhibition of the pulse generator. Additionally, pulse generator damage is possible if sufficient energy is coupled into it. Use of electrocautery within 4-5 centimeters of the implanted pacemaker can cause a direct coupling of RF energy through the lead and electrode to the cardiac muscle, producing burns or possible ventricular fibrillation.

Continuous monitoring of blood pressure and pulse should be instituted in all procedures where the use of electrocautery is contemplated. The ground plate of the electrocautery system should be placed in a manner to minimize current flow through the pacing system. A specific example is a TUR; during this procedure, the ground plate should be placed low on the buttocks or strapped to the thigh.

(2) Diathermy–A pacemaker patient should not receive this form of therapy. Very intense fields of microwave energy are involved and reactions of all sensing pulse generators are unpredictable. Total or virtually complete inhibition of the pacing circuitry is possible; however, no damage will result to the circuitry during the exposure.

(3) Microwave Ovens–Ovens, both in the home and in commercial use, in good condition and used as intended, will not affect the InterLith. Any microwave appliance which does not exceed federal guidelines of 0.5 milliwatts/cm² leakage at a point 2.5 cm. from the appliance will not affect the InterLith. However, appliances have been discovered which emit radiation in excess of 200 times these guidelines. The possibility of interference from such defective appliances does exist. The pulse generator will not be damaged by such exposure.

(4) Defibrillation–All implanted unipolar pulse generators regardless of manufacturer, can be damaged by cardiac defibrillation. Additionally, the presence of an implanted pacemaker system can increase the amount of cardiac muscle damage which results from defibrillation.

(5) Home Electrical and Gasoline Powered Appliances–Certain electrical and gasoline powered appliances can cause inhibition of an implanted cardiac pacemaker system. Pacemaker patients should be warned about the possibilities of pulse generator inhibition from some electric razors, most notably the rotary types, hand-held electric drills, power saws, and other appliances containing brush motors.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. The patient diagnosis and prognosis may indicate the type of pacemaker therapy used by the physician.

Body rejection phenomenon have been reported from the use of implanted cardiac pacemakers. These include local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism and cardiac tamponade.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541

ALDACTONE®
(spironolactone) 25 mg. tablets

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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San Juan, Puerto Rico 00936

Address medical inquiries to:
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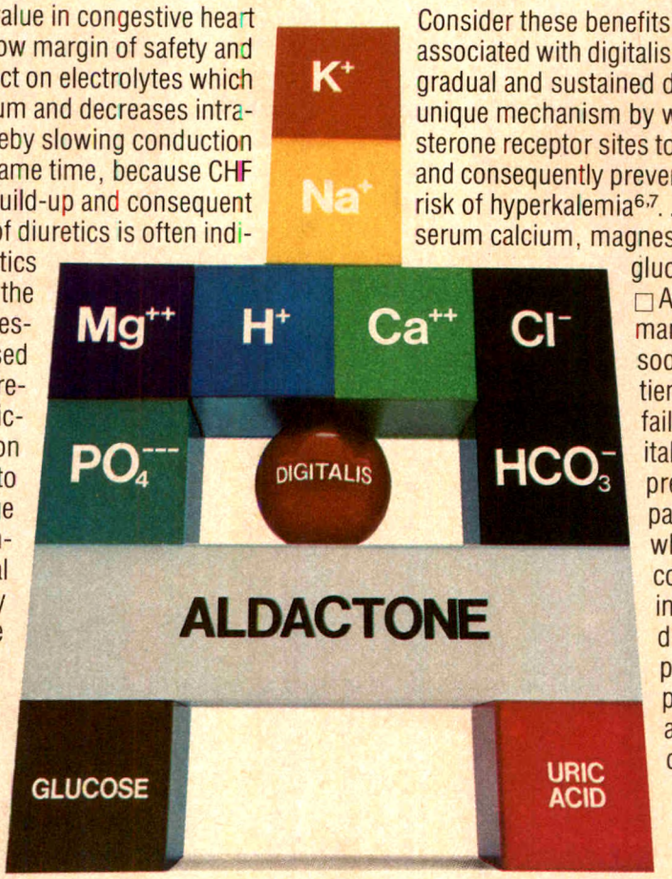
Box 5110
Chicago, Illinois 60680

719

The Delicate Balance.

Unfortunately, electrolyte imbalance is often a problem during digitalis therapy. And most diuretics worsen the problem.

Despite its therapeutic value in congestive heart failure, digitalis has a narrow margin of safety and toxic levels produce an effect on electrolytes which increases intracellular sodium and decreases intracellular potassium, thereby slowing conduction in cardiac tissues. At the same time, because CHF encourages sodium build-up and consequent edema, concomitant use of diuretics is often indicated. □ Use of most diuretics can increase problems for the patient on digitalis, and excessive loss of potassium caused by potent diuretics is a frequent cause of digitalis toxicity.[1,2] Potassium depletion sensitizes the myocardium to digitalis and can set the stage for serious cardiac arrhythmias even with normal dosage.[3] □ Clearly, any diuretic choice should be carefully analyzed for its effect on electrolyte balance. Thiazides, for example, can induce hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.[4] They can also decrease uric acid excretion and impair glucose tolerance. In treatment with furosemide, too, fluid and electrolyte imbalance is the most common form of clinical toxicity.[5]



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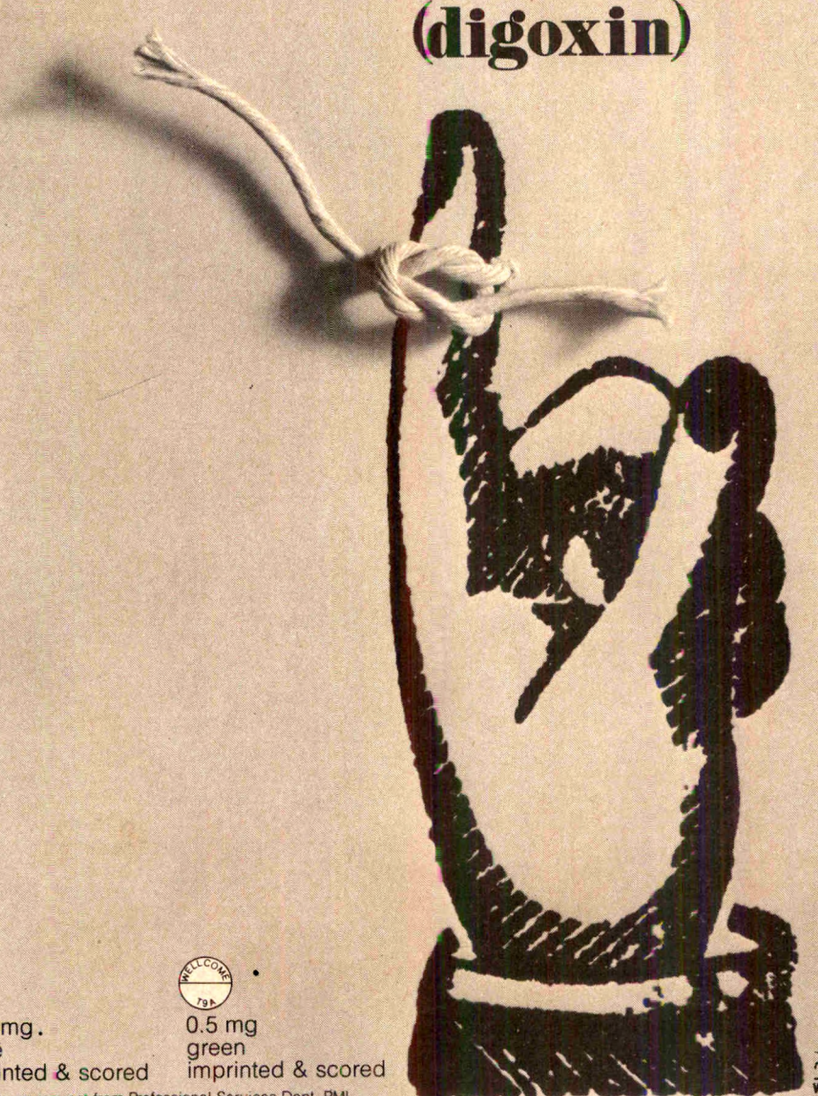

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CLINICAL STUDIES

Progressive Nature of Myocardial Injury in Selected Patients With Cardiogenic Shock

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To determine whether the extensive myocardial injury associated with cardiogenic shock in some patients results from a progressive rather than a discrete massive insult, a study was made of 15 selected patients who had cardiogenic shock within 48 hours of admission, 5 patients with hypovolemic shock without myocardial infarction and 11 patients with myocardial infarction without shock. Peak plasma MB creatine kinase (CK) activity was significantly higher in the seven patients with cardiogenic shock associated with initial infarction (213 international units [IU]/liter) than in patients with shock and previous infarction (98 IU/liter) and in patients with uncomplicated myocardial infarction (125 IU/liter). A prolonged time to peak MB CK activity (averaging 26 hours) and a plateau of elevated MB CK activity were seen in patients with shock associated with initial infarction. Because shock itself did not slow the rate of apparent MB CK disappearance, results obtained suggest that cardiogenic shock associated with initial infarction in selected patients results from progressive myocardial damage underlying continuing release of MB CK into the circulation. The findings are compatible with the concept that, in these patients, cardiogenic shock reflects a vicious cycle of spreading myocardial injury, progressive compromise of cardiac function, exacerbation of ischemia and perpetuation of myocardial damage.

Cardiogenic shock is an important cause of death in hospitalized patients with acute myocardial infarction. It appears to occur when 35 to 40 percent of the myocardium is destroyed.[1,2] Therapy designed to limit the extent of myocardial necrosis in patients with incipient or evolving shock has been relatively unsuccessful,[1–6] perhaps because irreversible injury is already so extensive when shock occurs that survival is precluded. On the other hand, the sequence of development of cardiac damage in such patients has not been thoroughly characterized, and the possibility that progressive injury amenable to interruption is responsible in at least some patients has not been excluded. Objective evaluation of therapy in relatively large numbers of patients with shock is difficult in part because of the high early mortality rate, complexity of medical

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management and relative rarity of the pure syndrome.

The present study was designed to determine whether cardiogenic shock in some patients results from progressive continuing damage to myocardium, reflected by prolonged discharge of MB creatine kinase (CK) into the blood, because interruption of such a process might permit survival of a mass of viable myocardium compatible with life. One consistent feature in autopsy specimens from patients who die with cardiogenic shock is the presence of multiple necrotic areas extending from a central area of infarction.[1,3] These morphologic characteristics are consistent with an initial area of central infarction underlying impairment of ventricular function in turn contributing to an expanding zone of ischemia and infarction. Some patients manifest shock early during the evolution of infarction, but others exhibit the condition later, often several days after admission. In this study, the time course of release of MB CK into plasma among patients with cardiogenic shock who survived for at least 18 hours after admission was compared with the time course in patients with uncomplicated infarction to determine whether progressive damage, reflected by prolonged release of MB CK, as opposed to a sudden massive insult to the heart, was a dominant feature of the syndrome in these selected patients.

The extent of myocardial injury is clearly one important determinant of mortality.[1,3,7–9] Unfortunately, enzymatic estimates based on analysis of serial changes in total plasma CK activity cannot be utilized in patients with shock because of potential release of CK from noncardiac sources such as underperfused skeletal muscle.[10,11] However, serial changes in plasma MB CK, an isoenzyme found virtually exclusively in myocardium in man, provide an index of damage sustained by the heart despite release of CK from noncardiac sources.[12] In studies with experimental animals, release of MB CK does not occur after transient ischemia but does occur when ischemia is sufficiently prolonged to cause necrosis, documented histologically.[13,14] MB CK in plasma does not increase in patients with angina, whereas a consistent increase is seen among patients with infarction.[15–17] Because the release of MB CK appears to be directly related to irreversible myocardial injury, analysis of plasma MB CK time-activity curves in patients with myocardial infarction and cardiogenic shock should help to determine whether the underlying process is progressive.

TABLE I

Therapeutic Agents* Administered to Patients in Each Category During the Course of the Study

	Patients With Shock	
	Without Previous Infarction (no. = 8)	With Previous Infarction (no. = 7)
Dopamine	8	7
Digoxin	5	4
Lidocaine	7	6
Morphine	8	7
Heparin	8	6
Diazepam	7	5
Furosemide	4	5

*No systematic differences were evident in the total doses of agents given to patients in the two categories.

Methods

Patients: The study group consisted of 31 selected patients, including 26 with acute myocardial infarction, admitted to the Barnes Hospital Cardiac Care Unit. Fifteen patients (8 men and 7 women with a mean age of 63 years) were selected because they had cardiogenic shock within 48 hours of admission, and 11 patients (8 men and 3 women with a mean age of 54 years) were selected because they exhibited an uncomplicated course without recurrent chest pain or clinical evidence of pulmonary edema or shock. Five additional patients had hypovolemic shock without myocardial infarction.

Diagnostic criteria for cardiogenic shock included blood pressure of 90/60 mm Hg or less for at least 1 hour, urinary output 20 cc/hour or less and pulmonary arterial occlusive pressure of 20 mm Hg or greater in the setting of acute myocardial infarction manifested by typical chest pain, new electrocardiographic Q waves and elevated plasma enzyme levels. The average interval from the onset of chest pain to admission was 4.3 hours (range 0 to 12). The initial electrocardiogram indicated that the site of infarction was anterior in nine, inferior in four and both inferior and anterior in two patients. Among patients with uncomplicated infarction, the electrocardiographic site was inferior in seven and anterior in four. The onset of shock occurred an average of 23 hours (range 8 to 48) after the onset of chest pain. Eight of the 15 patients with cardiogenic shock had no history or electrocardiographic criteria of previous infarction.

Patients with shock included in this study were managed exclusively with pharmacologic therapy and none required expansion of extracell volume beyond ordinary fluid requirements at any time during the study. Because patients with shock and initial infarction and those with shock and previous infarction were exposed to similar regimens (Table I), it is unlikely that the distinctive enzyme time-activity curves in the former (see Results) were due to pharmacologic effects on MB CK released from the heart or clearance from the circulation.

CK isoenzyme determinations: Blood samples for CK isoenzyme determinations were obtained every 4 hours through a peripheral indwelling venous cannula for 72 hours or until the patient died. Sampling was hourly for 10 hours and every 4 to 6 hours subsequently for 72 hours. Samples were collected in ethylene glycol-bis-tetraacetic acid (EGTA) (0.05 molar) and mercaptoethanol (0.05 molar) and assayed within 4 weeks for MB CK. Samples stored in this manner do not lose activity for at least 6 weeks.[18] Total CK activity was assayed spectrophotometrically,[19] both with and without creatine phosphate to exclude contributions to apparent activity from moieties besides CK. CK isoenzymes were assayed quantitatively by a batch adsorption procedure utilizing diethylaminoethyl (DEAE) glycophase glass beads.[20] Plasma MB CK time-activity curves were analyzed as previously described.[12]

Results

Clinical observations: The pulmonary arterial occlusive pressure among patients with cardiogenic shock averaged 23 mm Hg at the onset of shock and other hemodynamic findings were similar to those consis-

tently associated with the syndrome.[4,5] The clinical and hemodynamic data from patients with initial infarction complicated by shock, those with previous infarction antedating the infarct complicated by shock and those without shock are summarized in Table II.

All patients in this group eventually died, 12 during hospitalization (an average of 63.2 hours after the onset of chest pain, range 8 to 129 hours) and 3 much later (2, 3 and 6 months, respectively, after admission). All the patients who died during the initial hospitalization had further episodes of chest pain and a gradual deterioration of hemodynamic status. No patient with uncomplicated infarction died within the 6 months after admission and all patients with hypovolemic shock survived and were ultimately discharged from the hospital.

Plasma CK time-activity curves associated with shock and uncomplicated infarction: Table III lists peak plasma enzyme values and estimates of infarct size calculated from each patient's plasma MB CK time-activity curve, and Figure 1 compares results graphically among the three groups. Cumulated MB CK released in patients who had shock associated with an initial infarct averaged 64 gram equivalents (g-Eq), significantly higher than in patients with uncomplicated infarction (31 g-Eq) and in patients with shock and previous infarction (25 g-Eq). Patients with hypovolemic

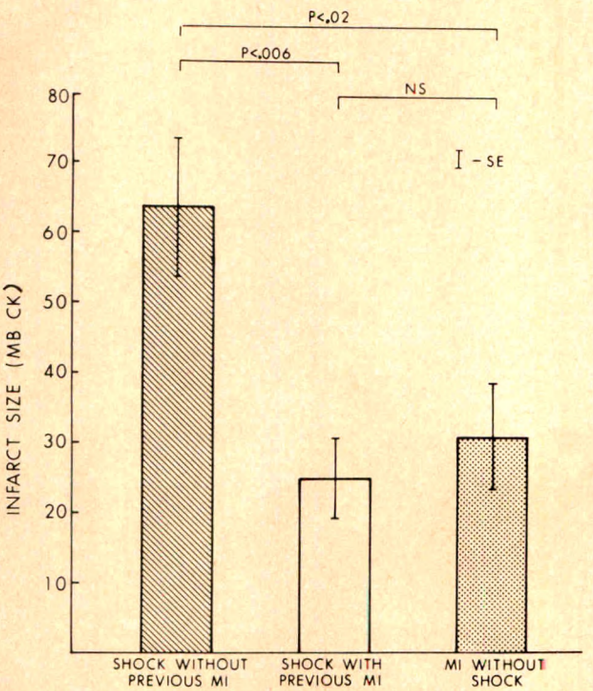

FIGURE 1. Estimates of cumulative MB creatine kinase (CK) released based on analysis of serial changes in plasma MB CK activity with results expressed as MB CK gram-equivalents. MI = myocardial infarction; P = probability; SE = standard error.

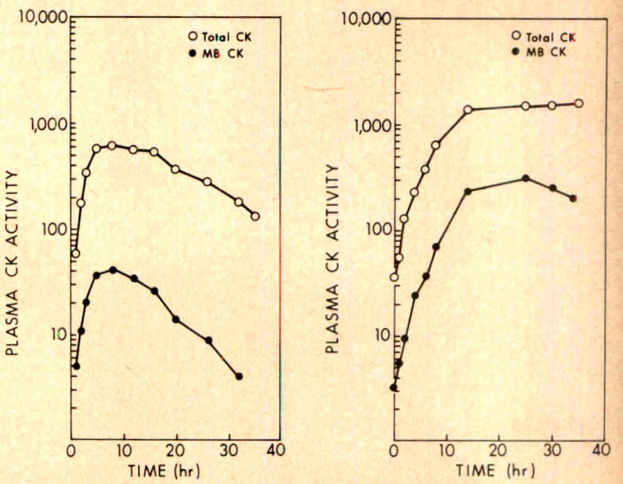

FIGURE 2. Serial changes in total plasma CK and MB CK activity in a representative patient with myocardial infarction without shock **(left)** and in one with shock associated with an initial myocardial infarction **(right).** In the patient with shock MB CK activity began to decrease while total plasma CK activity continued to increase during the interval from 27 to 36 hours after admission.

TABLE II

Selected Clinical Characteristics of Patients With and Without Shock

	Patients With Shock		Patients Without Shock
	Without Previous Infarction	With Previous Infarction	
Patients (no.)	8	7	11
Mean age (yr)	63	63	54
Electrocardiographic site of infarction (initial electrocardiogram)			
Anterior	5	6	4
Inferior	4	2	7
Interval (hours) from onset of infarction to			
Hospitalization	7.4	3.1	5.2
Shock	21.3	25.1	—
Death (average, if during this admission)	66.2	60.3	—
Pulmonary arterial occlusive pressure (mm Hg) (mean ± standard deviation)	24 ± 4	21 ± 3	—

TABLE III

Plasma MB Creatine Kinase (CK) Data

Case no.	Infarct Size (CK g-Eq)	Peak Plasma MB (IU/liter)	Time to Peak MB (hr)	Mean Rate of Rise (IU/liter per hour)	Peak to 75% Peak (hr)
		Patients With Shock Without Previous Myocardial Infarction			
1	108	250	24	10.4	2
2	57	140	37	3.8	10
3	60	160	32	5.0	20
4	25	120	30	4.0	6
5	30	390	17	22.9	4
6	87	320	25	12.8	6
7	64	147	35	4.2	4
8	77	180	11	16.4	27
Average	64	213	26	9.9	10
		Patients With Shock With Previous Myocardial Infarction			
9	25	80	21	3.8	4
10	34	120	16	7.5	5
11	26	105	17	6.2	4
12	7	20	10	2.0	10
13	50	180	12	15.0	2
14	9	48	17	2.8	4
15	22	130	7	18.6	1
Average	25	98	15	8.0	4
		Patients With Myocardial Infarction Without Shock			
16	30	215	13	16.5	8
17	45	120	14	8.6	4
18	31	82	9	9.1	8
19	20	40	8	5.0	6
20	97	137	15	9.1	10
21	13	40	10	4.0	9
22	9	56	6	9.3	5
23	32	25	11	2.3	8
24	19	55	14	3.9	8
25	12	30	9	3.3	3
26	36	125	13	9.6	7
Average	31	84	11	7.3	7

shock without myocardial infarction had no elevation of MB CK levels.

Plasma total CK and MB CK time-activity curves after uncomplicated myocardial infarction exhibit many similar characteristics. Typical examples are illustrated in Figure 2. The upstrokes of both curves and the times to peak activity are almost identical. However, the rate of decline is faster for MB CK and values return to baseline level much earlier. This probably reflects a more rapid disappearance rate for the MB isoenzyme.[21,22]

Total and MB CK time-activity curves in patients with acute myocardial infarction complicated by cardiogenic shock differ from those in patients with uncomplicated infarction (Fig. 2, Table III). The time of occurrence of peak plasma activity for both total and MB CK is later (24 hours after the onset of pain in the example in Fig. 2), averaging 26 hours in patients with shock and initial infarction compared with 11 hours in patients with uncomplicated infarction in this study and 10 hours in a previously reported series of 100 patients.[23] In spite of the prolonged time to peak activity in patients with shock, the mean rate of rise for both MB (Table III) and total CK was similar to that seen in patients with uncomplicated infarction and patients with shock and previous infarction ($P > 0.05$ for each comparison) (Table III). Among patients with shock with initial infarction, an initial normal rate of rise with a prolonged plateau of elevated MB CK activity, sometimes associated with secondary peaks, was characteristic. The time to peak activity in patients with shock and previous infarction was similar to that in patients with uncomplicated infarction.

Peak plasma MB CK activity averaged 21.3 international units [IU]/liter in the patients with cardiogenic shock with initial infarction, markedly exceeding activity in patients with shock and previous infarction (98 IU/liter) and in patients with uncomplicated infarction (125 IU/liter).

The mean elimination rate of MB CK among patients with shock was -0.0017 min^{-1}, the same as that observed in patients with uncomplicated infarction. Total CK (reflecting the preponderance of MM isoenzyme in the blood) remained elevated much longer than MB CK, probably reflecting continuing release of MM CK from skeletal muscle because of poor perfusion. In patients who survived sufficiently long for total CK to return to normal, the mean apparent elimination rate from blood (-0.001 min^{-1}) was similar to that in patients with uncomplicated infarction.[12] The slightly faster apparent elimination rate in patients with shock and initial infarction would of course tend to diminish the duration of the plateau.

Plasma MB CK curves in the three groups of patients were compared by analysis of the following values: (1) peak MB CK activity, (2) time to peak MB

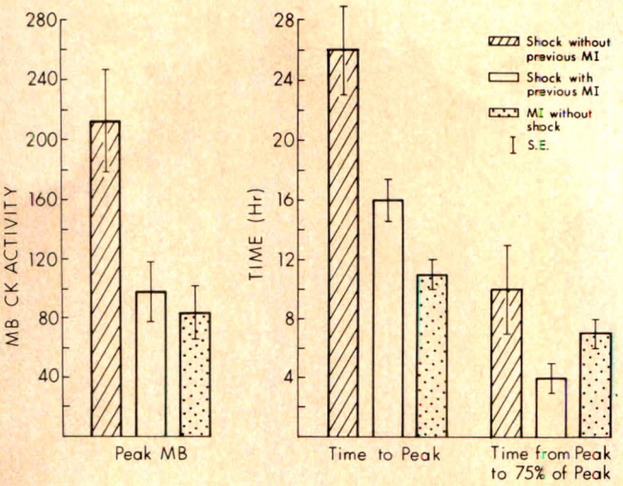

FIGURE 3. Characteristics of plasma MB CK time-activity curves in patients with shock associated with an initial myocardial infarction (MI), in those with shock associated with a new episode of infarction but a history of previous infarction and in those with myocardial infarction without shock. Peak plasma MB CK activity (IU/liter) was substantially higher in patients with shock associated with an initial infarction than in patients in the other two groups. A similar trend is evident in the interval during which plasma MB CK activity continued to rise after admission (time to peak). Although plasma MB CK activity decreased from peak values somewhat more slowly in patients with shock associated with an initial infarction **(right),** suggesting some continued release of MB from the heart after the time of occurrence of peak activity, the average rate of decrease was not significantly different from that seen in patients with myocardial infarction without shock.

CK, and (3) time required for MB CK to decline from peak to 75 percent of peak (Fig. 3). Peak plasma MB activity was highest in patients with shock with initial infarction and the time to peak MB was substantially longer in these patients than in patients with shock and previous infarction and those with uncomplicated infarction. The time required for MB CK to decline to 75 percent of peak value appeared to be slightly greater when shock occurred with initial infarction, but not significantly.

The relation between the time of onset of cardiogenic shock and the time of occurrence of peak plasma MB CK activity is illustrated in Table IV. In three of the eight patients with shock and initial infarction, shock occurred after MB CK had reached its peak.

Discussion

Continuing myocardial injury as a cause of prolonged rise of MB CK: Our results show that patients with cardiogenic shock after initial infarction have a prolonged rise of MB CK in contrast to the rise in patients with cardiogenic shock with a new episode after previous remote infarction or those with uncomplicated myocardial infarction. The prolonged rise of MB CK may be due to several factors including slow release of enzyme clustered within an extensive zone of necrosis with markedly decreased blood flow and, alternatively, continuing release of CK resulting from progressive and continuing myocardial damage. Presumably, entrapped enzyme would have an increased path length for diffusion with consequently delayed appearance in blood. It is not possible in the clinical setting to definitively determine which, if either, of these processes predominates. However, the evidence appears to favor continuing myocardial necrosis. If decreased regional flow were responsible for the prolonged MB CK upstroke in patients with shock without previous myocardial infarction, one would expect to see a similar effect on the upstroke in patients with previous infarction who have shock with a new episode. However, this was not the case. In fact, the interval preceding peak MB CK was not significantly different from that in patients with uncomplicated infarction. Furthermore, three of the patients with shock associated with an initial infarction did not have shock until after the occurrence of peak plasma MB CK activity.

TABLE IV

Relation Between Time of Occurrence of Peak MB Creatine Kinase (CK) Activity and the Onset of Shock in Patients Without Previous Infarction

Case no.	Time to Peak MB (CK) (hours)	Time to Shock (hours)
2	37	22
3	32	4
4	30	27
6	25	19
8	11	6
1*	24	48
5*	17	31
7*	35	40

* In these three patients, in contrast to the other five, shock occurred after the time of occurrence of peak MB CK activity.

Studies in experimental animals[24,25] have shown that CK is inactivated in lymph and that occlusion of cardiac lymphatics induced during myocardial infarction results in a 50 percent decrease of the amount of CK appearing in blood. If there were sequestration of enzyme in an entrapped zone of myocardium in patients with shock, presumably enzyme would be in contact with lymph for a prolonged interval, local degradation of CK would be enhanced and the amount of enzyme appearing in blood would therefore be decreased.

Other factors affecting MB CK time-activity curve: The shape of the plasma MB CK time-activity curve depends not only on the rate of release but also on the MB CK disappearance rate. A marked reduction in the elimination rate could simulate prolonged release and lead to sustained elevations of plasma MB activity.[22,26] In experimental animals, CK disappearance rates determined after intravenous injection of purified canine myocardial CK were not altered substantially by hemodynamic changes simulating those associated with acute myocardial infarction such as marked tachycardia, reduction of cardiac output by 67 percent, marked reduction of celiac arterial blood flow or bilateral occlusion of the renal arteries.[21] Furthermore, elimination rates were minimally affected by therapeutic doses of many drugs used in managing patients with complicated myocardial infarction.[27] The mean MB elimination rate in this study in patients with cardiogenic shock without previous infarction was $-0.0017\ min^{-1}$, a value similar

to that in patients with shock and previous infarction (-0.0016 min^{-1}) and in those with uncomplicated infarction (-0.0016 min^{-1}). Thus, as in the case in studies in experimental animals, profound hemodynamic disturbances including reductions in renal blood flow were not associated with apparent alterations of CK elimination rates.

Our results support the concept that the development of cardiogenic shock in patients with initial infarction is associated with massive myocardial damage.[1,2] Cumulated MB CK released estimated from analysis of MB CK time-activity curves was nearly twice as large in patients with shock as in those with uncomplicated infarction or those with previous infarction and shock developing with a new episode of infarction. Development of shock with cumulated MB CK release of apparently modest extent in patients with previous infarction may be due to the cumulative effects of multiple infarction on left ventricular function.

Estimates of cumulated enzyme release related to extent of infarction: Estimates of cumulated enzyme release based on analysis of serial changes in total CK activity correlate closely with early acute mortality,[9,28] the incidence of early ventricular arrhythmia,[29] alterations in left ventricular function,[6,30,31] changes in ventricular compliance and histochemical estimates of the extent of infarction.[28] Until recently, enzymatic estimates in patients with cardiogenic shock have been impractical because of the lack of precise quantitative assay techniques for plasma MB CK activity.[32] In our study, a recently developed adsorption procedure employing glycophase glass beads[20] was used for quantitative evaluation of activity. The sensitivity of this method is 2 IU/liter or less and its reproducibility is ±5 percent.

It is not surprising that estimates of cumulated enzyme released based on MB CK levels in patients with cardiogenic shock with initial infarction were twice as large as those in patients with uncomplicated infarction, because morphologic estimates of the extent of infarction in patients with shock are also large.[1,3] Although poor correlations between enzymatic and morphologic estimates of infarct size have been reported by some authors, allegedly because of variation of flow and washout, remarkably good correlations (variance of 0.71, $r = 0.86$) are obvious when the high background values (from noncardiac sources) are subtracted from the data (Table 10 in Reference 33). This observation suggests that variances are due more to the contribution from high background CK than from flow-dependent effects. If larger infarcts are associated with proportionately less release of CK, results in our study would be biased against the demonstrable clear separation of patients with shock from those with uncomplicated infarction based on analysis of plasma MB CK curves.

Clinical implications: Our view that the prolonged elevation of plasma MB CK activity in selected patients is due to progressive myocardial necrosis is in keeping with results of morphologic studies demonstrating large areas of central necrosis with multiple regions of necrosis apparently developing later.[1,3] The prolonged duration of release of MB CK reflected by delayed peak activity may be due to a vicious cycle of continuing progressive necrosis, compromised cardiac function, exacerbation of ischemia due to progressive reduction in coronary perfusion, additional myocardial damage and perpetuation of the cycle. Thus, in some patients who manifest shock with an initial infarction after admission to the hospital and who survive for at least 18 hours, interruption of progressive deterioration may be possible if favorable interventions can be implemented before a critical mass of myocardium has been destroyed.

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Hemodynamics and Coronary Angiography in Idiopathic Hypertrophic Subaortic Stenosis

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One hundred eighteen patients with idiopathic hypertrophic subaortic stenosis were studied with cardiac catheterization and coronary arteriography. In 112 a gradient across the left ventricular outflow tract was present in the resting state. Seventeen of the 61 patients who had right heart catheterization had a mild resting gradient across the right ventricular outflow tract, that was considered clinically and hemodynamically insignificant. Ninety-five patients (80 percent) had a left ventricular end-diastolic pressure greater than 10 mm Hg; 60 percent had mitral regurgitation that was of mild degree in most cases. Almost 20 percent had coexistent coronary atherosclerosis (25 percent incidence rate in subjects aged 40 years or older). Patients with associated severe coronary atherosclerosis had a lower intraventricular gradient at rest than other patients. Coronary atherosclerosis appears to be a coincidental condition. The need for objective evaluation of the coronary circulation is emphasized.

Idiopathic hypertrophic subaortic stenosis is frequently recognized and diagnosed in adulthood. The symptoms often simulate those of atherosclerotic heart disease.[1–3] Gulotta et al.[4] were among the first to present objective hemodynamic and angiographic proof of the coexistence of the two entities. Reports of large series of cases of idiopathic hypertrophic subaortic stenosis referred rather vaguely to atherosclerosis, mainly because the status of the coronary circulation was not objectively defined in most patients.[1–3,5] The real prevalence of atherosclerotic heart disease in this condition remains unknown. In this study we analyzed the hemodynamic and angiographic findings in 118 patients with idiopathic hypertrophic subaortic stenosis studied with retrograde catheterization and selective coronary arteriography and assessed the prevalence of coexisting atherosclerotic heart disease.

Material and Methods

Patients: The records of the Cardiac Laboratory from January 1961 to January 1975 were reviewed. One hundred eighteen cases of idiopathic hypertrophic subaortic stenosis were diagnosed on the basis of a combination of clinical and angiographic features specified by Braunwald et al.[1] and the presence at cardiac catheterization of a dynamic subaortic obstruction of the left ventricular outflow tract either at rest or after drug stimulation. The patients included 78 men (66 percent) and 40 women. Seventy-six percent of the patients were aged 40 years or more and 48 percent were 50 years or more. Angina pectoris was the main indication for cardiac catheterization in 59 patients (50 percent). The other patients were studied because of syncope, lightheadedness, palpitations, dyspnea, heart murmurs, abnormal electrocardiogram or a combination of these findings. All patients had a complete physical examination, chest X-ray film, 12 lead electrocardiogram and routine laboratory analysis the day before cardiac catheterization. Nine patients were receiving propranolol (average dose 118 mg/day), and 34 were taking digitalis before the procedure, generally because the presence

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of idiopathic hypertrophic subaortic stenosis was not suspected by the referring physician. Use of these drugs was discontinued 2 days before the catheterization.

Cardiac catheterization procedures: All the patients underwent left heart catheterization by brachial approach in the postabsorptive state under light sedation with diazepam. The usual procedure consisted of advancing the catheter to the ascending aorta and then into the left ventricle. A pullback from the apex of the left ventricle toward the outflow tract and the aorta was routinely performed. Some patients had retrograde catheterization of the left atrium with a regular Sones catheter or the Shirey left atrial catheter[6] and the pullback was performed from the left atrium to the aorta. In 69 patients with or without a spontaneous intraventricular gradient, isoproterenol was administered through the arterial catheter in a bolus dose of 2 to 10 μg. Usually 2 or 3 μg was injected and if the heart rate increased significantly, the catheter was repositioned at the apex or in the left atrium and the pullback performed again. When no significant increase in heart rate occurred, a second injection of a larger dose of isoproterenol was administered. In 19 patients a pullback was performed after inhalation of amyl nitrite. After this was accomplished, selective coronary arteriograms using the Sones technique[7] were obtained in all but four very young patients with normal origin of the right and left coronary arteries as indirectly visualized by opacification of the aorta. A left ventriculogram was performed in the right anterior oblique projection and in most cases repeated in the left anterior oblique projection. The left ventricular end-diastolic pressure was measured at high sensitivity and at a paper speed of 50 mm/sec at the beginning of the procedure before any medication was administered or dye injected. The presence of mitral regurgitation was detected and estimated with use of left ventricular angiography and classified as mild, moderate or severe by subjective evaluation. A complete analysis of the ventriculograms in this series is the subject of another study in progress.

Right heart catheterization studies, usually performed before the retrograde study in 61 patients (51.7 percent), consisted in most cases of pressure measurements in the pulmonary wedge position and pullback recordings through the pulmonary valve, right ventricle and tricuspid valve. In two patients a pullback from the pulmonary artery toward the right atrium was repeated after administration of isoproterenol.

Statistical analysis was performed using the chi-square test. A probability (P) value of <0.05 was considered significant. The data were processed with use of a computer (PDP 15 Digital Equipment Corporation).

Results

Table I summarizes the hemodynamic and angiographic findings. All patients included in this series had a gradient across the outflow tract of the left ventricle either spontaneously or induced with isoproterenol or amyl nitrite.

Spontaneous left ventricular gradient: One hundred twelve patients (95 percent) had a gradient at rest. In 71 patients (60 percent) the gradient was mild (50 mm Hg or less), in 27 patients (23 percent) moderate (51 to 99 mm Hg) and in 14 patients (12 percent) severe (100 mm Hg or greater). Moderate and severe gradients were more frequent among younger patients (Fig. 1). There was no difference between women and men in severity of obstruction. There was no significant difference between the gradient in patients on a regimen of propranolol or digitalis and that in the remaining patients. Two patients with a spontaneous gradient of 90 and 112 mm Hg, respectively, were receiving 160 mg of propranolol daily before the catheterization.

TABLE I

Cardiac Catheterization and Angiographic Findings

	Patients	
	no.	%
Spontaneous gradient across LVOT (mm Hg)		
≤50	71	60.2
51—99	27	22.9
≥100	14	11.9
Total	112	95.0
Isoproterenol-induced gradient across LVOT (mm Hg)		
≤50	21	17.8
51–99	22	18.6
≥100	26	22
Total	69	58.4
Amyl nitrite-induced gradient across LVOT (mm Hg)		
≤50 mm	8	6.8
51–99	8	6.8
≥100	3	2.5
Total	19	16.1
Right heart catheterization		
Gradient across RVOT	17	14.4
No gradient	44	37.3
Total	61	51.7
Left ventricular end-diastolic pressure (mm Hg)		
≤10	23	19.5
11–15	30	25.4
16–20	18	15.3
≥21	47	39.8
Total	118	100
Mitral regurgitation		
Mild	51	46.6
Moderate	11	9.3
Severe	4	3.3
Total	70	59.2
Coronary circulation		
Anomalous origin of circumflex artery	1	0.9
Mild CAD (mild irregularities)	7	5.9
Moderate CAD (<70% stenosis)	7	5.9
Severe CAD (70% or more stenosis)	9	7.6
Total	24	20.3

CAD = coronary artery disease; LVOT = left ventricular outflow tract; RVOT = right ventricular outflow tract.

Isoproterenol-induced gradients: A repeat pullback procedure was performed in 69 patients after administration of isoproterenol. In approximately one third of the patients with a mild spontaneous gradient there was no change after isoproterenol, but in the remaining two thirds a more significant gradient developed. Seven of 10 patients with a moderate gradient at rest had a higher gradient and 3 had an unchanged gradient after isoproterenol. Four of the 69 patients who received isoproterenol were taking propranolol before catheterization and had a mild spontaneous gradient; two of these had a mild and two a moderate gradient after isoproterenol.

Amyl nitrite-induced gradients: A repeat pullback procedure after amyl nitrite inhalation was performed in 19 patients. Seven of 15 patients with a mild gradient at rest manifested more severe obstruction after amyl nitrite; 6 had a moderate and 1 a severe gradient. Two

of the four patients with a moderate gradient at rest manifested severe obstruction after amyl nitrite; the gradient in the other two was unchanged.

Right ventricular outflow tract gradient: Seventeen patients (27.8 percent of those with right heart catheterization) had a right ventricular outflow tract gradient of 5 to 25 mm Hg (average 12 mm Hg). A pullback procedure, repeated after administration of isoproterenol in two patients, revealed a 12 mm Hg gradient in one and an increase from 6 to 34 mm Hg in the other. There was no apparent correlation between right and left ventricular gradients. The prevalence of right-sided obstruction was actually less in patients with a moderate or severe left-sided gradient.

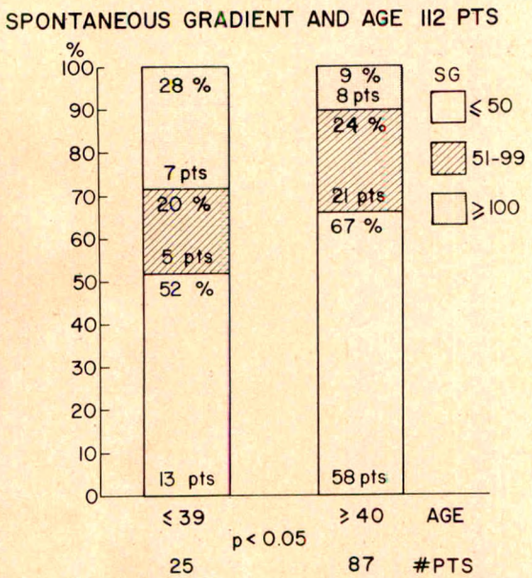

FIGURE 1. Moderate and severe spontaneous gradients (SG, in mm Hg) in 112 patients with idiopathic hypertrophic subaortic stenosis. Higher gradients are more frequent among younger patients. Age (yr) and the number of patients (#PTS) are given on the **abscissa.** p = probability.

Left ventricular end-diastolic pressure (Table I): There was no difference in pressure in patients younger than 40 years and those 40 years and older. Propranolol intake before catheterization apparently did not influence the level of left ventricular end-diastolic pressure. There was a positive correlation between this pressure and the degree of spontaneous gradient (Fig. 2) with an increasing prevalence of moderate and severe gradients among patients with greater end-diastolic pressure. Lower end-diastolic values correlated with lower gradients; almost 80 percent of patients with a normal or mildly elevated pressure (15 mm Hg or less) had a mild gradient. Higher pressure levels had less predictive value; 51 percent of patients with a left ventricular end-diastolic pressure of 21 mm Hg or more had a mild gradient.

Mitral regurgitation (Table I): The male to female ratio in patients with mitral regurgitation was similar to that of the whole group. There was no difference in the prevalence of mitral regurgitation among the various age categories. Its prevalence in the three subgroups of patients with a gradient at rest is depicted in Figure 3. There was a positive correlation between these variables: More than 70 percent of patients with a moderate or severe gradient had mitral regurgitation ($P < 0.05$). The presence of mitral insufficiency was not useful in predicting the severity of left ventricular obstruction because 55 percent of all patients with mitral regurgi-

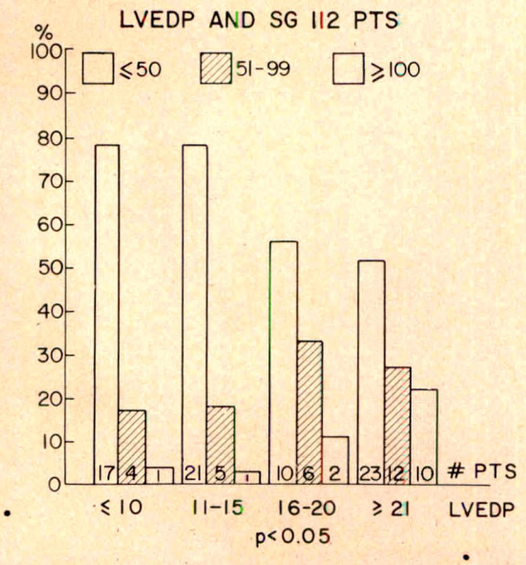

FIGURE 2. Relation between the level of left ventricular end-diastolic pressure (LVEDP in mm Hg) and spontaneous gradients (SG) in the resting state in 112 patients. The correlation is positive. Gradients are shown as ≤50 **(open bars),** 51 to 99 **(hatched bars)** and ≥100 **(dotted bars)** mm Hg.

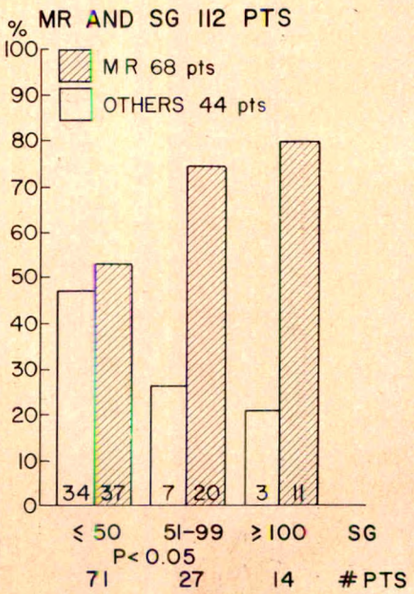

FIGURE 3. Mitral regurgitation (MR) in relation to spontaneous gradients (SG) in the resting state. The correlation is positive. Values on the **abscissa** indicate the three subgroups of spontaneous gradients and the number of patients. P = probability.

tation had only a mild gradient. The previous intake of propranolol did not seem to influence the presence or severity of mitral regurgitation. This valve defect was not related to the presence of severe coronary atherosclerosis: Five of nine patients with 70 percent or more stenosis of the luminal diameter of one of the major coronary arteries had mild mitral regurgitation and four had a competent mitral valve. Figure 4 shows the relation between mitral regurgitation and left ventricular end-diastolic pressure. There is a greater prevalence of regurgitation among patients with a pressure of 16 mm Hg or greater than in those with a lower pressure; this difference was statistically significant.

Coronary circulation: Only one patient had a congenital anomaly: an anomalous origin of the circumflex artery from the proximal segment of the right coronary artery (Table I). Seven patients had minor irregularities of the lumen and were classified as having mild coronary artery disease. Seven patients had obstruction of 30 to 60 percent of the luminal diameter of one or more of the major coronary arteries and were considered to have moderate coronary artery disease. The nine patients with 70 percent or more stenosis of at least one major coronary artery were classified as having severe coronary artery disease. The site and distribution of the obstructive lesions were not different from those observed in patients with isolated coronary atherosclerosis. Seven of the nine patients with coexisting cardiomyopathy and severe coronary atherosclerosis had angina pectoris (Table II); this symptom did not differ from angina pectoris secondary to isolated coronary atherosclerosis. Two of the nine patients with severe coronary atherosclerosis had no gradient at rest, six had a gradient of less than 50 mm Hg and one a gradient of 55 mm Hg. These gradients were less severe than the gradients in the remaining patients ($P < 0.05$). Four of the eight patients given isoproterenol had a higher degree of obstruction; in two the gradient increased to 60, in one to 160 and in one to 180 mm Hg.

Twenty-three patients, 12 men and 11 women, had coronary artery disease. The severity of the disease was similar in men and women. Ten of the 11 women were 50 years or older, whereas 7 of the 12 men were in this age group. The 11 women represented 21.5 percent of all women with idiopathic hypertrophic subaortic stenosis included in this series. Patients 7, 8 and 9 (Table II) had severe obstruction of the major coronary arteries with good distal runoff and were advised to undergo myocardial revascularization surgery. Patient 9 had atypical chest pain and refused the operation. The other two had, respectively, class II and class III angina before operation and underwent coronary bypass revascularization procedures without complications. Because the gradients were mild, neither patient underwent myotomy. Both were free of angina 2 and 3 years later.

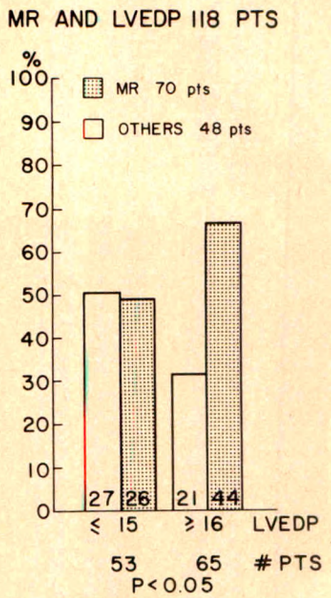

FIGURE 4. Mitral regurgitation (MR) in relation to left ventricular end-diastolic pressure (LVEDP). The prevalence of mitral regurgitation is greater in patients whose pressure is equal to or higher than 16 mm Hg.

Discussion

Ventricular outflow tract obstruction: Ninety-five percent of the patients in our series had left ven-

TABLE II

Findings in Nine Patients With Obstructive Cardiomyopathy and Severe Coronary Atherosclerosis

Case no.	Coronary Stenosis (%)			Pressure (mm Hg)			Q Wave	Akinesia
	RCA	LCx	LAD	SG	IG	EDP		
1	—	70	—	0	60	15	0	No
2	80	—	50	0	41	40	0	No
3	100	20	40	20	30	20	aVL, V_6	No
4	50	60	90	40	160	22	0	No
5	10	40	70	10	180	32	0	No
6	—	—	70	55	NR	27	0	No
7	100	70	30	30	40	3	II, III, aVF	No
8	90	80*		16	32	12	0	No
9	100	90	80	20	60	6	0	No

* Left main trunk.

EDP = left ventricular end-diastolic pressure; IG = isoproterenol-induced intraventricular gradient; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NR = not recorded; RCA = right coronary artery; SG = spontaneous intraventricular gradient.

tricular outflow tract obstruction in the basal state, 40 percent having an intraventricular gradient greater than 50 mm Hg. We found no difference between men and women in severity of such obstruction but, although we had a relatively small number of young patients, they had a higher left ventricular gradient than older patients. The possibility that young patients with severe obstruction would die before reaching an older age does not seem to be supported by the work of Braunwald et al.,[1] who found that only 3 of the 10 patients dying from idiopathic hypertrophic stenosis had serious ventricular obstruction documented by a gradient of more than 70 mm Hg in the basal state. There are conflicting reports regarding the relation between resting gradient, symptoms and prognosis. The scope of our study did not permit an explanation of the higher gradient in younger patients. The use of propranolol (average dose 118 mg/day) up to 2 days before cardiac catheterization did not influence the magnitude of obstruction recorded. This observation suggests that the beta adrenergic receptors were not effectively blocked because of the disappearance of the blockade after 48 hours of drug withdrawal before the catheterization or the relatively small dose, or both. Most of the patients on digitalis therapy were receiving digoxin and its effect was probably minimal after 48 hours of withdrawal; no difference in gradient was found between these patients and the rest of the group. Isoproterenol was effective in producing or increasing the intraventricular gradient in two thirds of the patients when administered at the time of the hemodynamic study. Amyl nitrite seemed to be less effective: only half of the patients given amyl nitrite by inhalation showed a clear-cut increase in gradient.

A right ventricular outflow tract gradient was present in 28 percent of the patients who had right heart catheterization. The gradients were generally small and never greater than 25 mm Hg. This mild obstruction showed no correlation with the severity of the obstruction of the left ventricle and probably does not have important hemodynamic or clinical implications. Similar observations were reported in two large series of patients.[1,2]

Elevated left ventricular end-diastolic pressure was a frequent finding. Normal or mildly elevated left ventricular end-diastolic pressure was associated with a mild gradient. However, high left ventricular end-diastolic pressure (21 mm Hg or greater) coexisted in more than half the patients with a mild gradient, suggesting that increased stiffness of the myocardium is the most important determinant of this alteration. Deterioration of clinical status has been associated with greatly increased left ventricular end-diastolic pressure regardless of the degree of outflow tract obstruction. This abnormality was recognized as one of the more consistently observed hemodynamic alterations in five patients who died suddenly.[2]

Mitral regurgitation, most frequently of mild degree, occurred in about 60 percent of the patients. No difference in age or sex of the affected patients was apparent. This finding occurred in 70 percent of the patients with a moderate or severe gradient. A significant correlation with left ventricular end-diastolic pressure was observed. Swan et al.[2] reported no significant difference in the incidence of mitral regurgitation among patients whose clinical course was stable, improved or deteriorated in their follow-up study of 85 patients. In a previous report,[1] mitral regurgitation was found in 14 of 31 patients who underwent ventriculography. These patients were older and more disabled than those without regurgitation. However, their disability may have been related to their significantly higher left ventricular end-diastolic pressure (22.1 mm Hg in the patients with mitral regurgitation versus 14.4 mm Hg in those with a competent valve. Furthermore, in these patients no differences were found in the contour of the left atrial pressure, suggesting that the increase in left atrial pressure reflects increased stiffness of the left ventricle primarily and is probably only slightly influenced by the presence of mitral regurgitation.

Associated coronary artery disease: The only congenital anomaly encountered in the coronary circulation was anomalous origin of the circumflex artery in one patient. Its presence in this series appears to be coincidental. Angiographic evidence of moderate to severe coronary atherosclerosis was found in 13.5 percent of our patients. Gulotta et al.[4] previously described 10 patients (9 of whom were men) with coexistent idiopathic hypertrophic subaortic stenosis and coronary artery disease who were studied because of disabling angina. We were initially surprised that 11 of our 23 patients with coronary artery disease were women, a greater proportion of women than in the patients without coronary disease ($P < 0.05$). However, these 11 women represented 27.8 percent of the total number of women studied and this prevalence rate does not differ significantly from the 29 percent rate of significant coronary artery disease in 414 women between 45 and 49 years of age previously studied in our laboratory.[8] The latter were studied because of chest pain, arrhythmias, conduction disturbances, dyspnea, syncope or congestive heart failure and were found to have no evidence of idiopathic hypertrophic subaortic stenosis or valve disease. Kasparian et al.,[9] studying 63 women with chronic valve disease whose ages were comparable with those of the women in our series, found a 22.2 percent incidence of coronary atherosclerosis, very similar to ours. It is believed then that the coronary artery disease in our cases of idiopathic hypertrophic subaortic stenosis is coincidental. The presence of the latter does not seem to influence the development of coronary atherosclerosis. Gulotta et al.,[4] in their patients with coexistence of both entities, reported gradients similar to those of our subgroup with both diseases. These gradients were milder than those of the patients without severe coronary atherosclerosis. The ventriculograms did not show in any of our patients evidence of akinesia that would indicate that the smaller gradients were caused by deterioration of left ventricular function after previous myocardial infarction. The association of severe muscle hypertrophy and increased ventricular mass together with reduced coronary flow might account for a reduced ventricular performance and lower than expected gradients. This question re-

mains speculative and requires prospective investigation in larger series of patients with coexistence of the two diseases.

The importance of a clear definition of the status of the coronary circulation in patients with idiopathic hypertrophic subaortic stenosis should be stressed. Not all the patients with both diseases have typical angina pectoris. On the other hand, the finding of a spontaneous or provoked intraventricular gradient in an adult patient with angina should not be considered sufficient to explain the symptomatology. Objective evaluation of the coronary circulation with selective coronary arteriography is warranted to rule out the coexistence of coronary atherosclerosis.

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Anuloaortic Ectasia: Angiographic, Hemodynamic and Clinical Comparison With Aortic Valve Insufficiency

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Thirty-five patients with angiographically diagnosed anuloaortic ectas.a were compared with 18 patients with isolated aortic valve insufficiency to study differences between the presentation, hemodynamic or angiographic findings and clinical course in the two groups. The maximal aortic root diameter in anuloaortic ectasia was 7.6 ± 2.4 cm (mean ± 1 standard deviation) versus 4.2 ± 0.6 in aortic insufficiency. Dissection was a common complication of anuloaortic ectasia (44 percent) but was not seen in aortic insufficiency. Neither the size nor the configuration of the aortic aneurysm was a reliable predictor of dissection. Despite surgical therapy, patients with anuloaortic ectasia have a worse prognosis than those with aortic valve insufficiency.

Dilatation of the aortic ring and ascending aorta in patients without features of Marfan's syndrome or other known causes for aortic dilatation was reported in 1961 by Ellis et al.,[1] who originated the term anuloaortic ectasia. Since then, many investigators[2–9] have reviewed the natural history and surgical treatment of this condition and its pathogenetic relation to cystic medial necrosis of the aorta. However, there have been few attempts to quantify the size and shape of the aortic root in anuloaortic ectasia and to relate these features to the clinical course or surgical results. At the time of initial presentation, most patients with anuloaortic ectasia have evidence of aortic insufficiency, yet there are few data comparing these patients with patients who have pure aortic valve insufficiency. Because of these considerations we performed a retrospective study to answer the following questions:

1. Are there significant differences in the presentation, hemodynamics, aortic size and shape and clinical course of patients with anuloaortic ectasia or aortic valve insufficiency?
2. Can the shape and size of the dilated ascending aorta be used to predict the clinical course or incidence of dissection in patients with anuloaortic ectasia?
3. How reliable is cineangiography in detecting dissection in anuloaortic ectasia?

Patients and Methods

Patients with anuloaortic ectasia: Hospital records from 1960 to 1976 were reviewed for patients with angiographically diagnosed anuloaortic ectasia. Before 1967 large "cut films" were used to study these patients; since 1967 cineangiography has been used exclusively. All cineangiograms were reviewed by one of us (D.L.). The configuration of the ascending aorta was traced and measured with correction for magnification made using an accompanying grid. We defined the maximal aortic diameter as the largest dimension of the ascending aorta, proximal to the origin of the brachiocephalic vessels, measured in a plane perpendicular to both walls.

The angiographic severity of the aortic regurgitation was judged on a scale of 1+ to 4+ as follows: Grade 1+, a trace of contrast material in the outflow tract

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of the left ventricle, but the ventricular cavity never outlined. Grade 2+, opacification of the entire ventricle in diastole with regurgitant contrast material, but complete emptying with each systole. Grade 3+, progressive opacification of the ventricle with each beat. Grade 4+, the ventricular cavity rapidly and clearly outlined, the density of contrast material greater in the ventricle than in the aorta, and contrast medium remaining in the left ventricle for at least five beats after the end of injection.

History, physical examination, chest X-ray film, electrocardiogram and cardiac catheterization results were obtained from hospital records. The ascending aorta was considered to be dilated in the posteroanterior chest X-ray film if its border was greater than 1.5 cm to the right of the right border of the vertebral bodies. Electrocardiographic criteria of Romhilt and Estes[10] were used for the diagnosis of left ventricular hypertrophy. Surgical and pathologic reports were reviewed. The diagnosis of aortic dissection was verified at the time of surgery or at postmortem examination. Surviving patients receiving only medical therapy were therefore excluded from statistical computations on the accuracy of the diagnosis of dissection. Return clinic visits, calls to local physicans or to patients and their families provided the follow-up data.

Patients with pure aortic insufficiency: As a comparison group, consecutive patients with pure aortic valve insufficiency (aortic gradient less than 10 mm Hg and no other cardiac lesions) were selected from a review of the computerized cardiac catheterization records from 1972 to 1976. No attempt was made to match for age, sex or functional class, but there proved to be no significant differences in these variables between the patients with insufficiency and anuloaortic ectasia. The procedures for review of the hospital records, angiograms and follow-up data in the patients with insufficiency were similar to those used in the group with anuloaortic ectasia.

Statistical analyses between and within groups were made using the Freeman-Tukey test and a table of proportionalities. Differences of less than 0.05 were considered statistically significant. All results are expressed as the mean ± 1 standard deviation.

Results

Patient population: During the 16 years from 1960 to 1976 there were 34 patients with a diagnosis of anuloaortic ectasia. Six of these patients had other clinical characteristics permitting a diagnosis of Marfan's syndrome. A comparison group of 18 patients with pure valve aortic insufficiency was found during the 4 year period from 1972 to 1976 in which computerized catheterization records were available. The average age of patients with anuloaortic ectasia at the time the diagnosis was confirmed at angiography was 48 ± 14 years, an average not significantly different from that of patients with aortic insufficiency (38 ± 13 years). Both groups had equivalent limitations in physical activity (68 percent in functional class I to II in anuloaortic ectasia, 78 percent in aortic insufficiency; difference not significant). Men constituted more than 70 percent of the patients in both groups.

Symptoms: Although 18 percent of patients with anuloaortic ectasia had symptoms for less than 1 week, 40 percent were symptomatic for more than 6 months. No patient in the group with aortic insufficiency had symptoms for less than 1 week. Chest pain was the most common symptom in patients with anuloaortic ectasia, occurring in 71 percent, but it was present in only 28 percent of patients with aortic insufficiency ($P < 0.001$). This symptom was a sensitive but nonspecific predictor of the occurrence of aortic dissection in patients with anuloaortic ectasia; it was present in 11 of 11 patients whose dissection was surgically confirmed but also present in 12 of 16 patients in whom dissection was later excluded at surgery. Dyspnea was a prominent symptom in both anuloaortic ectasia and aortic insufficiency, occurring in more than 65 percent in both groups; palpitations and syncope were uncommon, occurring in less than 15 percent in both groups.

The group with aortic insufficiency thus showed two distinct differences in symptoms: (1) No patient had acute onset of symptoms. (2) Chest pain was an uncommon symptom.

Physical examination: All patients with anuloaortic ectasia and aortic valve insufficiency in this series had aortic regurgitation. Patients in both groups had comparable amounts of aortic regurgitation as judged angiographically: grades 3+ and 4+ occurred in 61 percent of those with aortic insufficiency and in 62 percent of those with anuloaortic ectasia. Peripheral signs of aortic regurgitation (bounding peripheral pulses and positive Duroziez sign) tended to be less common in patients with anuloaortic ectasia than in those with aortic insufficiency (31 versus 78 percent, $P < 0.01$).

In 5 of 10 patients with anuloaortic ectasia judged clinically to have mild regurgitation, angiography revealed severe regurgitation (grade 3+ to 4+). This disparity between the clinical signs of mild regurgitation and the angiographic assessment of severe aortic regurgitation was not noted in any patient with aortic insufficiency.

Chest X-ray film and electrocardiogram: Visualization of a dilated ascending aorta in the chest X-ray film was helpful when suspecting the diagnosis of anuloaortic ectasia. Sixty-five percent of patients with anuloaortic ectasia had this sign compared with only 28 percent of patients with aortic insufficiency.

Left ventricular hypertrophy was a common electrocardiographic diagnosis in both groups. Cardiac arrhythmias were present in only one patient with anuloaortic ectasia and in no patient with aortic insufficiency.

Hemodynamic data: Hemodynamic findings were slightly better in the group with aortic insufficiency than in the patients with anuloaortic ectasia (higher cardiac index and lower left ventricular end-diastolic pressure). Hemodynamic values did not help in predicting the eventual outcome (medical or surgical, or both) in patients with anuloaortic ectasia. Mortality in the subgroup of patients with anuloaortic ectasia whose cardiac index was below normal was not significantly greater than that in patients with this diagnosis whose cardiac index was normal or above (33 and 30 percent, respectively; difference not significant). Likewise, an increased left ventricular end-diastolic pressure in patients with anuloaortic ectasia was not predictive of an increased mortality (33 percent mortality rate in those

TABLE I

Angiographic Description of Aortic Root in Anuloaortic Ectasia and Aortic Valve Insufficiency and Correlation With Clinical Course

	Shape of Aneurysm			Aortic Dimensions (cm)								
				Total Group			With Dissection			No Dissection		
	Cases (no.)	Incidence Rate (%)	Mortality Rate* (%)	no.	Mean	Range	no.	Mean	Range	no.	Mean	Range
A. Anuloaortic Ectasia												
Pear-shaped enlargement	19	56	32	18	8.6 ± 2.4‖	5.7–14.0	5	9.0 ± 2.8†	5.7–14.0	13	8.5 ± 2.3†	6.1–15.0
Dilatation of sinus of Valsalva	2	6	50	2	5.4	5.3–5.4	1	5.3	. . .	1	5.4	. . .
Diffuse dilatation	9	27	33	8	5.9 ± 0.6‖	5.0–6.9	3	5.9 ± 0.8‡	5.0–6.9	5	4.9 ± 0.5‡	5.3–5.9
Not available	4	12	50	6	. . .	. . .	2	. . .	. . .	4	. . .	. . .
Total group	34	. . .	35	28	7.6 ± 2.4¶	4.8–15.0	9	7.6 ± 2.8§	5.0–14.0	19	7.6 ± 2.3§	5.3–15.0
B. Aortic Valve Insufficiency												
. . .	18	. . .	11	18	4.2 ± 0.6¶	3.3–5.5	0	. . .	. . .	18	. . .	. . .

* Total mortality (medical or surgical therapy, or both).
† Difference not significant: Pear-shaped enlargement with dissection versus no dissection.
‡ Difference not significant: Diffuse dilatation with dissection versus no dissection.
§ Difference not significant: Total group with dissection versus no dissection.
‖ $P < 0.005$: Pear-shaped versus diffuse enlargement.
¶ $P < 0.005$: Total group: Anuloaortic ectasia versus aortic insufficiency.

whose pressure was 20 mm Hg or less, 30 percent mortality in those whose pressure was 12 mm Hg or less; difference not significant). Although the ejection fraction in both groups was similar (anuloaortic ectasia 52 ± 3 percent, aortic insufficiency 55 ± 2 percent; difference not significant), the prognosis during the follow-up period was much more favorable in the group with insufficiency (Table I).

Angiographic data: The mean maximal aortic root diameter in anuloaortic ectasia was 7.6 ± 2.7 cm, although there was a wide range (4.8 to 15.0 cm). Aneurysms occurred in three characteristic shapes: pear-shaped enlargement (56 percent), diffuse symmetric dilatation (27 percent) and dilatation limited to the sinuses of Valsalva (6 percent). The maximal aortic root diameter was significantly larger in the subgroup of patients whose aorta was pear-shaped than in the other two groups (Table I). The size of the aneurysm did not correlate with the severity of the aortic regurgitation as judged angiographically (Fig. 1). In aortic insufficiency the maximal aortic root diameter was significantly smaller (mean 4.2 ± 0.6 cm with a narrow range). The maximal aortic root diameter measured similarly in a group of 14 adult patients without aortic disease was 2.5 to 3.5 cm (mean 2.9 ± 0.3 cm). These values are comparable with echocardiographic measurements of the normal aortic root.[11]

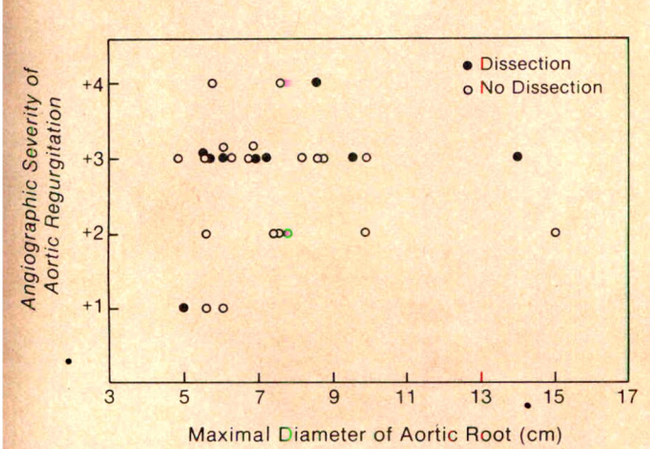

FIGURE 1. Graph relating the maximal diameter of the aortic root in patients with anuloaortic ectasia to the occurrence of aortic dissection and to the angiographic severity of the aortic insufficiency.

There were no differences in the aortic dimensions in the subgroups of patients with and without other features of Marfan's syndrome. The mean maximal aortic root diameter in patients with Marfan's syndrome was 7.5 ± 1.5 cm, a value not significantly different from that in the subgroup of patients with anuloaortic ectasia not having Marfan's syndrome. Five of the six patients with Marfan's syndrome had a pear-shaped aneurysm; the sixth had diffuse enlargement.

Recent aortic root dissection was confirmed at surgery in 44 percent of patients with anuloaortic ectasia but was never seen in aortic valve insufficiency. A diagnosis of dissection could be made cineangiographically in only 4 of 11 patients in whom dissection was later surgically confirmed. Clinical suspicion of dissection proved to be more accurate than cineangiography; seven of nine clinically suspected cases were later confirmed at surgery. The size and shape of the aortic aneurysm were not helpful in predicting the occurrence of dissection (Table I and Fig. 1). Recent dissection was found in two of the three patients with Marfan's syn-

drome who were surgically treated. Dissection was present in 41 percent (9 on 22) of those without other signs of Marfan's syndrome.

Clinical course: *Patients with anuloaortic ectasia* were followed up for an average of 37 months (range 1 month to 6 years) from the time of angiographic confirmation of the original diagnosis until the present study or until death. Six patients were lost to follow-up. Surgery was performed in 73 percent of patients (25 of 34) with anuloaortic ectasia. Of this surgically treated group, 40 percent (10 of 25) subsequently died. The size of the aneurysm in patients who died ranged from 5 to 14 cm. Aortic valve replacement alone was performed in six of these patients and combined with grafting of the ascending aorta in two patients. Two patients were treated with only an aortic graft.

The cause of death in anuloaortic ectasia appears to fit into two distinct categories: sudden death and progressive congestive heart failure.

One half of the deaths in the surgically treated group were secondary to progressive heart failure occurring 8 days to 2 years after operation; the other half occurred suddenly 8 days to 4 years after surgery. Autopsy in two patients who died suddenly after surgery revealed aortic dissection or rupture. There were two deaths among the nine patients with anuloaortic ectasia who did not have surgery. In the subgroup of six patients with Marfan's syndrome, three surgically treated patients are alive; there has been one death in the three patients not having surgery.

Patients with aortic valve insufficiency were followed up an average of 14 months (range 1 to 37 months). Four patients were lost to follow-up. Sixty-one percent of patients (11 of 18) in the group with aortic insufficiency had surgery; there have been 9 long-term survivors in this group. The two deaths that occurred were caused by progressive congestive heart failure and bacterial endocarditis.

Discussion

Anuloaortic ectasia represents an uncommon but serious cause of aortic insufficiency. This study compares the clinical, hemodynamic and angiographic features of this syndrome with the more commonly occurring aortic valve insufficiency and documents marked differences between patients with the two conditions.

Differences in ascending aortic dilatation: Dilatation of the aortic root is an angiographic finding common to both diseases. In patients with aortic valve insufficiency the dilatation diffusely involved the ascending aorta distal to the aortic valve but was of modest degree. Dilatation limited to the sinuses of Valsalva or pear-shaped enlargement of the aortic root was not seen. The limited extent of maximal aortic root dilatation in aortic insufficiency is reflected in the infrequent recognition of enlargement of the aortic root in the chest X-ray films in this disease. In contrast, patients with anuloaortic ectasia showed moderate to severe enlargement of the ascending aorta, although there was a wide range of maximal aortic root diameters. Although aortic root enlargement in anuloaortic ectasia is typically described as "pear-shaped," [2] we found three distinct shapes. Pear-shaped enlargement was most common, but one third of the patients had diffuse symmetric enlargement of the aortic root, and in a smaller group the dilatation involved only the sinuses of Valsalva. Visualization of the aortic dilatation in the chest X-ray film was common in anuloaortic ectasia.

Differences in symptoms: The clinical presentation in anuloaortic ectasia and aortic valve insufficiency showed distinct differences. Patients with aortic insufficiency had a generally insidious disease and heart failure was the most common reason for referral; chest pain was distinctly uncommon. Although a significant percent of patients with anuloaortic ectasia presented with an acute illness, the majority had a more chronic condition. Chest pain was the most common presenting symptom, but it was nondescript and rarely suggestive of angina or dissection. Our findings differ from those of Layman and Wang,[2] who found chest pain to be uncommon in anuloaortic ectasia. However, in neither series did chest pain accurately predict the occurrence of dissection.

Differences in estimate of severity of aortic regurgitation: The physical examination in patients with aortic valve insufficiency and anuloaortic ectasia also showed surprising differences. In the group with insufficiency, clinical grading of aortic regurgitation correlated well with the angiographic estimate of its severity. In patients with anuloaortic ectasia, clinical judgment as to the degree of insufficiency was less accurate. Less than half of the patients with anuloaortic ectasia having angiographically severe aortic regurgitation (grade 3 to 4) had peripheral signs of aortic insufficiency. The exact mechanism of this difference remains unclear, but we speculate that the large volume of the aneurysm in anuloaortic ectasia may act as a sump to dampen peripheral transmission of the initial and reflected pressure waves.

Correlation of size of aortic aneurysm with incidence of dissection and degree of aortic insufficiency: Aortic dissection was a common finding in anuloaortic ectasia but was not seen in aortic valve insufficiency. Because of the often catastrophic nature of this complication, we reviewed the angiographic data of patients with anuloaortic ectasia in an attempt to find predictors of this event. Because dilatation of the aortic root is a universal finding in this syndrome, we postulated that the occurrence of dissection or rupture might correlate with the maximal diameter of the aneurysm.

Our data suggest that dissection of the aorta and the clinical course of anuloaortic ectasia cannot be reliably predicted from the maximal diameter of the ascending aorta. Although the aortic diameter was much larger in patients with anuloaortic ectasia than in those with aortic insufficiency, there was no difference in aortic root size in patients with or without dissection. Other investigators have also noted a general lack of relation between dissection and the size of the aneurysm although the exact size of the aneurysm has not been

quantitated.[3] Brown et al.,[12] using echocardiographic techniques, were also unable to correlate the size of aneurysm with the amount of regurgitation. A similar lack of correlation between size of aneurysm and degree of aortic insufficiency was confirmed in our study. The aortic configuration was also not an accurate predictor of dissection. Patients with diffuse enlargement of the ascending aorta had a mortality rate equivalent to the rate of those with pear-shaped enlargement even though the mean aortic diameter in the former group was significantly smaller.

Diagnosis of aortic dissection: Although dissection is a common complication and was frequently suspected clinically, this suspicion was often difficult to confirm. Because quantitation of the degree of aortic insufficiency was desired, most diagnostic studies were performed using cineangiography. Cineangiography proved to be an insensitive technique to detect dissection: Only 4 of 11 cases diagnosed preoperatively were later confirmed at surgery. There are at least three possible explanations for this poor diagnostic performance: (1) cineangiography does not yield the equivalent radiologic resolution as cut films, the standard technique for the angiographic diagnosis of dissection[13–15]; (2) aortic root injections are usually performed in only one projection, and the site of dissection might therefore have been poorly visualized; and (3) frequently the extent of dissection in anuloaortic ectasia is small, often not extending beyond the brachiocephalic vessels, thus making detection difficult.

Prognosis and mode of death: Our study reemphasizes the serious nature and poor prognosis of anuloaortic ectasia.[16,17] Although most patients were treated surgically, 36 percent died during the follow-up period. The survival statistics of those patients with Marfan's syndrome were not worse than those without other signs of systemic disease. These findings are consistent with those of Wagenvoort et al.,[3] who were unable to distinguish pathologically between the aorta of patients with and without Marfan's syndrome. Nasrallah et al.[18] also emphasize the guarded outlook for patients with Marfan's syndrome despite surgical intervention. In their series of 30 patients with anuloaortic ectasia treated surgically, the 5 year mortality rate was 57 percent.

A disturbing proportion of the deaths in our series were sudden (50 percent). The absence of evidence of arrhythmias in the electrocardiogram (33 of 34) and the finding of redisssection and rupture at postmortem examination suggest that dissection may be the reason for sudden postoperative deaths. This is not entirely unexpected because pathologic findings of cystic medial necrosis are not confined to the ascending aorta but are found in other areas of the aorta and in other vessels containing large amounts of elastic tissue in the media. Recent studies[19] suggest that the medial defect that predisposes to dissection is not specific for anuloaortic ectasia but represents an injury and repair process common to the normal aging aorta. However, it occurs earlier and is quantitatively more severe in this syndrome.

Implications: Our study reaffirms the diagnostic and therapeutic dilemmas that anuloaortic ectasia presents to the physician. We were unable to find significant predictors of aortic dissection, a major complication in this disease. Surgical therapy, although preferred, does not have a uniformly good prognosis. Although the survivors in our study are symptomatically well, these findings suggest that their long-term prognosis must still be considered guarded.

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Left Ventricular Performance in Patients With Atrial Septal Defect: Evaluation With Noninvasive Methods

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Eighteen patients with an atrial septal defect (Group I) and 45 patients whose defect had been repaired (Group II) were studied with echocardiography and systolic time intervals. All patients in Group I had an increased right ventricular diameter (mean 24.5 mm/m^2) that showed a direct linear relation to the size of the shunt (Qp/Qs ratio). In Group II the right ventricular diameter was significantly smaller (mean 15.6 mm/m^2) ($P < 0.001$). The left ventricular diameter measured less than the mean normal value in 13 of the 18 patients in Group I (mean 23.2 mm/m^2) and was significantly larger in the 45 in Group II (mean 27.7 mm/m^2) ($P < 0.001$).

Comparison of systolic time intervals in Groups I and II showed that patients in the former group had shorter mean left ventricular ejection time index (LVETI) (407.9 versus 420.8 msec, $P < 0.05$), a longer mean preejection period index (PEPI) (140.9 versus 126.7 msec, $P < 0.001$) and a higher mean ratio of preejection period to ejection time (PEP/LVET) (0.39 versus 0.33, $P < 0.001$). A direct linear relation existed between both the preejection period index and the PEP/LVET ratio and the size of the shunt (Qp/Qs) in Group I. In three patients the abnormal systolic time intervals were consistent with mildly diminished left ventricular performance preoperatively but promptly returned to normal postoperatively. However, echocardiographic assessment revealed that left ventricular wall contractility was normal or hyperdynamic in all cases.

The mildly diminished overall left ventricular performance as shown by systolic time intervals appears to be related to the volume overload of the right ventricle and to the concomitantly diminished volume of the left ventricle rather than to any impairment of myocardial contractility. After closure of the defect the size of the ventricle and its performance return to normal.

Abnormality of left ventricular function in patients with an atrial septal defect has been reported by several investigators.[1–5] It has also been detected in patients after surgical closure of the defect, and in some cases it has first become manifest postoperatively.[2,3,6,7] However, its incidence and its relation to right ventricular dysfunction in the pathophysiology of atrial septal defect both before and after surgery are not known. The availability of noninvasive means for obtaining accurate measurements of both ventricles and for assessing left ventricular performance has permitted convenient screening of patients in an attempt to cast further light on these questions. This study was undertaken for this purpose, using the combined techniques of echocardiography and the determination of systolic time intervals.

Subjects and Methods

Patients: Fifty-five patients with an ostium secundum atrial septal defect were studied; 10 had an unrepaired defect, 37 were examined only after surgical closure of the defect and 8 were studied both pre- and postoperatively. The 18

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TABLE I

Noninvasive Data and Shunt Measurements

	Mean Normal Values	Group I (mean ± 1 SD)	Group II (mean ± 1 SD)	*P* Value (I versus II)
Echocardiographic data				
RVD				
Adults (mm/m^2)	9	24.5 ± 5.7	15.6 ± 4.2	<0.001
Children (mm)	. . .	24.4 ± 3.6	19.6 ± 3.3	. . .
LVD				
Adults (mm/m^2)	26	23.2 ± 2.9	27.7 ± 3.4	<0.001
Children (mm)	. . .	32.2 ± 3.8	39.7 ± 6.1	. . .
ΔD%	35	36.0 ± 4.0	35.9 ± 4.0	NS
VCF (circumferences/sec)	1.3	1.36 ± 0.24	1.20 ± 0.16	NS
LV posterior wall				
Excursion (mm)				
Adults	12	13.9 ± 2.4	13.5 ± 2.1	NS
Children	. . .	10.6 ± 1.1	12.5 ± 2.8	. . .
Mean velocity (mm/sec)	41	46.6 ± 8.4	45.1 ± 7.2	NS
Normalized mean velocity (sec^{-1})	0.95	1.27 ± 0.27	1.00 ± 0.17	<0.001
Systolic time intervals (adults)				
QS_2I (msec)	547	548 ± 11.3	548 ± 17.1	NS
LVETI (msec)	415	408 ± 10.9	421 ± 15.2	<0.05
PEPI (msec)	132	141 ± 9.5	127 ± 11.5	<0.001
PEP/LVET ratio	0.35	0.39 ± 0.05	0.33 ± 0.05	<0.001
Shunt measurement				
Qp/Qs ratio	. . .	2.13 ± 0.86	2.22 ± 0.75	NS

ΔD% = percent shortening of left ventricular diameter; LVD = left ventricular diastolic diameter; LVET and LVETI = left ventricular ejection time and index; NS = not significant; *P* = probability; PEP and PEPI = preejection period and index; Qp/Qs = ratio of pulmonary to systemic flow; QS_2I = index of total electromechanical systole; RVD = right ventricular diastolic diameter; SD = standard deviation; VCF = mean rate of circumferential shortening.

patients with an unrepaired defect (Group I) included 13 adults aged 18 to 60 years (mean 31.8) and 5 children aged 4 to 12 years. The 45 patients with a closed defect (Group II) included 35 adults aged 18 to 56 years (mean 29.7) and 10 children aged 5 to 13 years. The patients in Group II were studied 10 days to 11 years postoperatively. The diagnosis of atrial septal defect had been confirmed at operation in each of these patients and total repair of the defect had been accomplished.

All patients with a closed defect had undergone cardiac catheterization before operation. Pressures were measured through a fluid-filled catheter system. Pulmonary and systemic flows were measured with the Fick oxygen method and shunt size was expressed as the ratio of pulmonary to systemic flow (Qp/Qs). Four of the 10 patients not yet operated on did not undergo catheterization, and the diagnosis of ostium secundum atrial septal defect was made on clinical grounds and confirmed with echocardiography.

Echocardiography: Complete echocardiographic study was performed in all the patients with a Unirad Series 100 echocardiograph utilizing a 2.25 megahertz, 1.3 cm diameter transducer focused at 7.5 cm. The recordings were made on a Honeywell 1858 fiberoptic recorder. The transducer was held in the third or fourth interspace just to the left of the sternum. The right and left ventricular diameters were measured, and the interventricular septal motion was assessed from recordings made with the ultrasonic beam directed so that the right ventricular anterior wall, the interventricular septum and the left ventricular posterior wall endocardium were clearly delineated in a position where the echoes from the inferior mitral valve apparatus (inferior edges of the leaflets or chordae tendineae) were evident. Right ventricular end-diastolic diameter was always measured with the patient supine. Gain adjustments were made so as to define properly the anterior wall, and the right ventricular diameter was measured from the endocardium of the anterior wall to the right side of the interventricular septum. Both the right and left ventricular end-diastolic diameters (Dd) were measured at the time of the peak deflection of the QRS complex. The left ventricular end-systolic diameter (Ds) was measured at the point of closest approximation of the interventricular septum and the posterior wall endocardial echoes in systole. The percent shortening of left ventricular diameter was calculated as [(Dd − Ds) × 100]/Dd. The mean rate of circumferential shortening was calculated, using the left ventricular ejection time (LVET) obtained from the carotid artery pulse tracing, as (Dd − Ds)/(Dd × LVET). The calculation of percent shortening of left ventricular diameter and mean rate of circumferential shortening was made only in patients with normal motion of the left side of the septum (posterior systolic excursion of at least 3 mm). Left ventricular posterior wall mean velocity was calculated as posterior wall excursion divided by left ventricular ejection time. The mean posterior wall velocity was divided by left ventricular end-diastolic diameter to obtain the normalized velocity. The normal values for the echocardiographic measurements are those reported by Feigenbaum[8,9] and Fogelman[10] and their co-workers.

Systolic time intervals: All patients had systolic time intervals measured from simultaneous electrocardiographic, phonocardiographic and carotid arterial pulse tracings recorded photographically at 100 mm/sec paper speed using an Electronics for Medicine VR-6 system, according to the methods described by Weissler[11] and Lewis[12] and their coworkers. The total electromechanical systole (QS_2), the left ventricular ejection time (LVET) and the preejection period (PEP) in the adult patients were corrected for heart rate employing linear regression equations and were expressed as their respective indexes (QS_2I, LVETI and PEPI).[11,12] The ratio of preejection period to left ventricular ejection time (PEP/LVET) was calculated using the uncorrected PEP and

TABLE II

Patients Studied Both Before (Preop) and After (Postop) Operation

Case no.	State	Age at Operation (yr)	Qp/Qs Ratio	RVD	LVD	ΔD%	VCF	LV Posterior Wall: Excursion	LV Posterior Wall: Mean Velocity	LV Posterior Wall: Normalized	PEP/LVET
1	Preop	20	3.25	33	19	...	...	14	64	1.9	0.44
	Postop 39 days			21	26	...		18	61	1.3	0.28
2	Preop	18	3.57	31	21	...	...	11	42	1.3	0.38
	Postop 14 days			20	29	34	1.13	12	40	0.9	0.29
	60 days			13	29	35	1.10	12	46	1.0	0.39
3	Preop	24	3.60	28	25	...	...	16	58	1.4	0.45
	Postop 14 days			19	29	47	1.67	18	64	1.3	0.33
4	Preop	25	2.94	24	23	...	...	12	44	1.1	0.48
	Postop 10 days			21	26	...	...	14	56	1.3	0.27
5	Preop	24	1.50	23	23	30	1.06	12	42	1.0	0.38
	Postop 24 days			18	25	...	...	14	59	1.4	0.41
	31 days			16	25	31	...	11	50	1.2	...
	60 days			16	25	33	1.32	11	45	1.0	...
6	Preop	21	1.36	19	23	...	...	11	41	0.9	0.36
	Postop 37 days			17	23	...	...	11	44	1.0	0.38
7	Preop	22	1.29	14	26	36	1.10	15	45	1.0	0.31
	Postop 35 days			16	26	33	1.26	13	49	1.1	0.36
8	Preop	5	1.47	(21 mm)	(27 mm)	33	1.44	10	38	1.4	...
	Postop 75 days			(22 mm)	(28 mm)	36	1.36	9	33	1.2	...

Abbreviations and units of measurements as in Table I.

LVET values. The normal range was taken to be ±2 standard deviations from the mean.* Statistical data were analyzed with the aid of a CBC CYBER 73 computer by calculation of means, standard deviations (SD) and correlation coefficients and use of Student's *t* test.

Results

The mean values of the noninvasive data and the shunt measurements for the patients in Group I (unrepaired atrial septal defect) and Group II (repaired atrial septal defect) are presented in Table I. Table II summarizes the data on the eight patients who were studied noninvasively both before and after surgical closure of the defect.

Clinical and hemodynamic observations: None of the patients showed clinical signs of congestive heart failure and all but one had normal sinus rhythm. The latter was a 60 year old woman, not operated on, who had severe mitral insufficiency due to a flail posterior mitral leaflet demonstrated echocardiographically as well as congestive heart failure and atrial fibrillation. This patient has been excluded from the statistical analyses. Other associated lesions included mild bilateral pulmonary arterial branch stenosis (one patient) and moderate pulmonary valve stenosis (two patients with a peak systolic gradient of 37 and 49 mm Hg, respectively, who underwent pulmonary valvotomy at the time of the atrial septal defect repair). In four patients an apical holosystolic murmur consistent with mitral insufficiency was heard postoperatively; no evidence of prolapse or other disease of the mitral leaflets was found on echocardiography in these or any other patients in this study. These patients were included in the study because statistical analysis revealed that their elimination yielded no significant differences in the results.

The size of the shunt, expressed as the ratio of pulmonary to systemic flow (Qp/Qs), ranged from 1.14 to 5.25. In six patients there was a large shunt, with a ratio of 3.0 or more; in 29 the ratio ranged from 1.8 to less than 3.0, and in 16 there was a small shunt of less than 1.8.

The right atrial mean pressure was normal in all but nine patients, in whom it ranged from 7 to 10 mm Hg. The left atrial mean pressure was slightly elevated (13 mm Hg) in one patient and normal in the rest. The right ventricular end-diastolic pressure was elevated above 8 mm Hg in only seven patients, and only two patients had pulmonary blood pressure of more than 35 mm Hg systolic. The left ventricular end-diastolic pressure was

* Because the published data on normal values for systolic time intervals related to heart rate and age in children are conflicting and are based on recording techniques different from those we used, the results of systolic time interval measurements in the children in this study are not given. However, because the apparatus and techniques we used are identical to those used by Weissler, we feel justified in applying his regression equations for adults to the adults in this study

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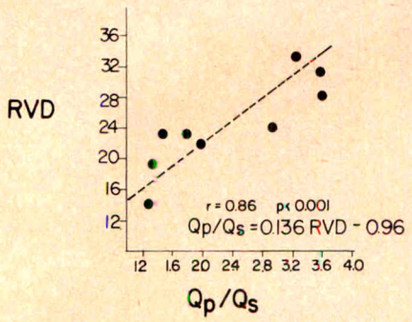

FIGURE 1. Direct linear relation between right ventricular diameter (RVD) (mm/m^2) and the size of the shunt expressed as the ratio of pulmonary to systemic flow (Qp/Qs) in the nine adults with unrepaired atrial septal defect in whom the Qp/Qs was measured.

less than 13 mm Hg in all 25 patients in whom it was measured.

Groups I and II did not differ significantly in patients' age or any hemodynamic value.

Right and left ventricular diameters: *The right ventricular diameter* was increased above normal in all patients in Group I. The extent of enlargement of the right ventricular diameter showed a direct and statistically significant relation to the size of the shunt (Fig. 1). Among the 45 patients in Group II the right ventricular diameter was normal in 12 and increased in 33. The mean right ventricular diameter per body surface area (adults) was significantly greater in Group I (24.5 mm/m^2) than in Group II (15.6 mm/m^2) (Fig. 2).

The left ventricular diameter was below normal in one patient and in the lower half of the normal range in the remaining patients in Group I. The mean left ventricular diameter per body surface area (adults) was significantly lower in Group I (23.2 mm/m^2) than in Group II (27.7 mm/m^2) (Fig. 3).

Each of the eight patients studied both before and after operation had a decrease in right ventricular diameter and an increase in left ventricular diameter after closure of the defect (Table II). The earliest postoperative examination in this group was performed 10 days after repair.

Interventricular septal motion: The motion of the left side of the septum was either flat or paradoxical in 11 of the 18 patients in Group I. The ratio of pulmonary to systemic flow in these patients ranged from 1.36 to 3.60 (mean 2.56). In 7 of the 18 patients normal motion of the left side of the septum was recorded; these patients all had a small shunt (ratio of 1.14 to 1.76, mean 1.43). Left-sided septal motion was normal in the 45 patients in Group II except for 6 patients in whom it was flat or paradoxical.

Left ventricular performance (Fig. 4): *Left ventricular posterior wall performance* as assessed with echocardiography (systolic excursion, mean systolic velocity and normalized mean velocity) was normal or hyperdynamic in all patients. The mean value for the normalized velocity was significantly greater in Group I than in Group II.

Overall left ventricular pump performance from echocardiographic measurements (percent shortening of left ventricular diameter and mean rate of circumferential shortening) can be assessed only in cases with normal movement of the left side of the interventricular septum. These measurements could thus be used only in a minority of the patients in Group I but in the majority of those in Group II. The measurements were

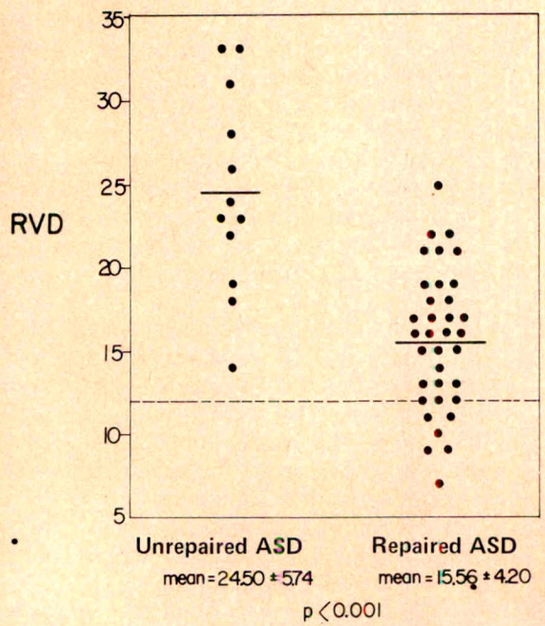

FIGURE 2. Distribution and mean values of the right ventricular diameter (RVD) (mm/m^2) in the adult patients with unrepaired and repaired atrial septal defect (ASD). The **area below the interrupted horizontal line** represents the normal range. p = probability.

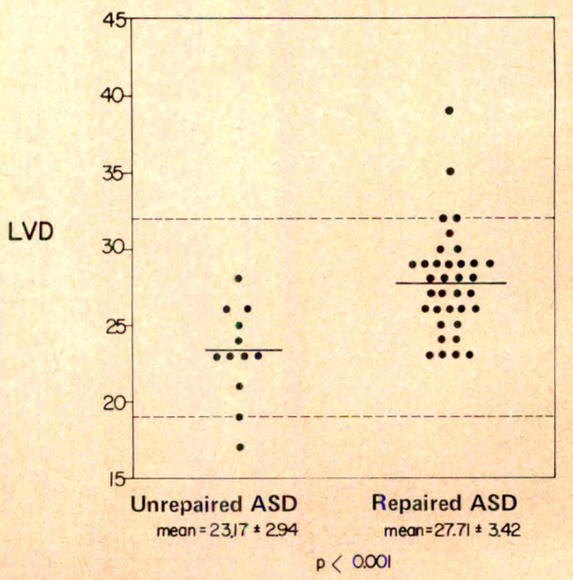

FIGURE 3. Distribution and mean values of the left ventricular diameter (LVD) (mm/m^2) in the adult patients with unrepaired and repaired atrial septal defect (ASD). The **area between the interrupted horizontal lines** represents the normal range.

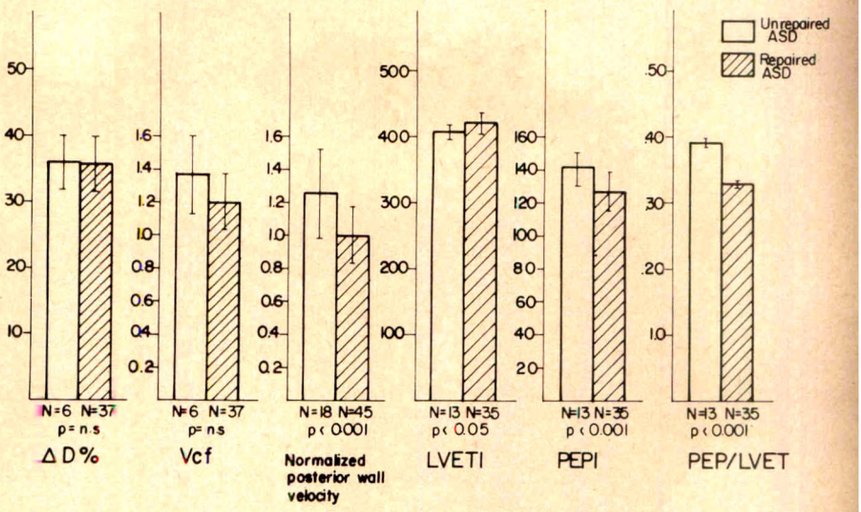

FIGURE 4. Mean values of measures of left ventricular performance in unrepaired and repaired atrial septal defect (ASD). ΔD% = percent shortening of left ventricular diameter; LVET and LVETI = left ventricular ejection time and index (msec); N = number of patients; n.s. = not significant; p = probability; PEP and PEPI = preejection period and index (msec); Vcf = mean rate of circumferential shortening (circumferences/sec).

normal or hyperdynamic in both groups with no significant differences between them.

Overall pump performances as assessed from systolic time intervals (adult patients) was normal in all patients in Group II. Patients in Group I had a shorter mean left ventricular ejection time index (LVETI), a longer mean preejection period index (PEPI) and a higher mean ratio of preejection period to ejection time (PEP/LVET) than patients in Group II, these differences being statistically significant (Fig. 4). Furthermore, in 3 of 13 patients in Group I (Cases 1, 3 and 4 in Table II), the systolic time intervals were abnormal and were consistent with mild impairment of left ventricular performance, which promptly returned to normal after operation. The postoperative changes in the systolic time intervals in these three patients, as well as the concomitant decrease in right ventricular diameter and increase in left ventricular diameter, are shown in Figure 5.

There was a highly significant correlation between the size of the shunt (Qp/Qs) and the preejection period index (PEPI) in patients in Group I (Fig. 6). A similarly significant correlation with the PEP/LVET ratio was found.

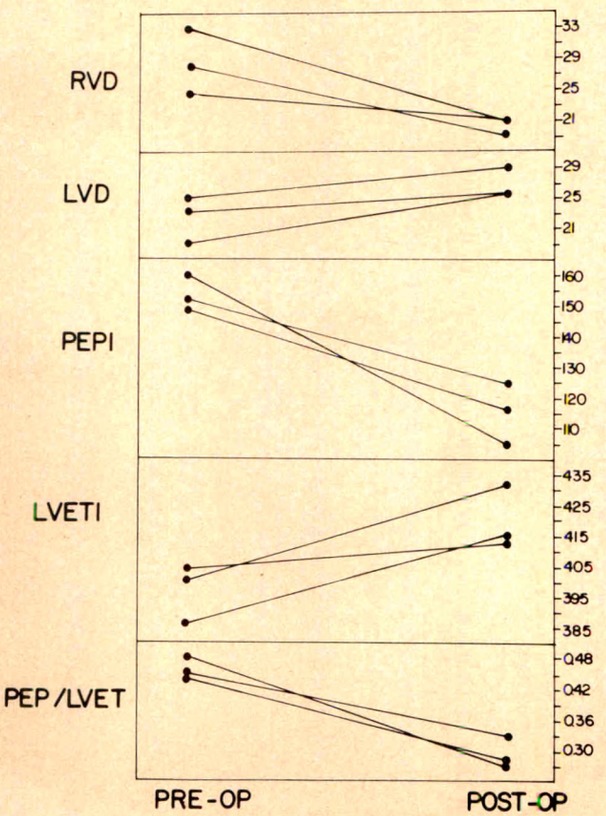

FIGURE 5. Changes that occurred after surgery in the three patients whose preoperative (PRE-OP) systolic time intervals were consistent with mildly diminished left ventricular performance. LVD and RVD = left and right ventricular diameters (mm/m^2); POST-OP = postoperative; other abbreviations as in Figure 4.

Discussion

Congestive heart failure commonly occurs with advancing age in patients with unrepaired atrial septal

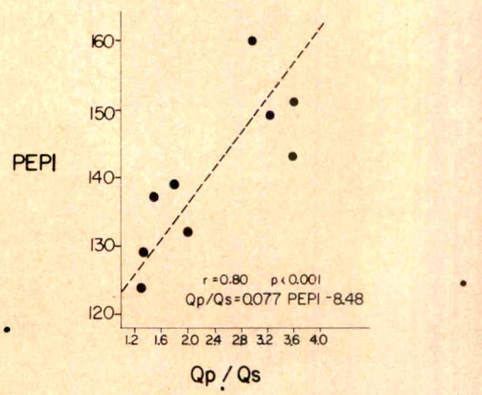

FIGURE 6. Direct linear relation between size of the shunt (Qp/Qs ratio) and preejection period index (PEPI) in the nine adults with unrepaired atrial septal defect in whom the Qp/Qs ratio was measured.

defect, but its pathophysiologic origin is not clear. Dexter[1] and Tikoff et al.[2] suggested that the long-standing left to right shunt may give rise to a hypoplastic left ventricle that eventually fails as a result of relative disuse and atrophy. Flamm et al.[4] on the other hand pointed out that the left ventricle fails in atrial septal defect only in association with right ventricular failure and apparently as a result of it. They postulated a generalized myocardial response to prolonged right ventricular volume overload, possibly on the basis of anatomic continuity of the major muscle bundles between the two ventricles or overall biochemical impairment of the myocardium.

The role of left ventricular dysfunction and its relation to right ventricular dysfunction in the pathophysiology of atrial septal defect therefore remain unclear. The situation after surgical closure of the defect is equally uncertain. Several reports[2,3,6,7] have noted cardiac dysfunction and congestive heart failure among postoperative patients, but most of these studies do not indicate whether the dysfunction involved the right ventricle alone or the left ventricle as well.

Echocardiography versus systolic time intervals in assessment of left ventricular performance: In this study we utilized echocardiographic measurements of right and left ventricular diameters and measures of left ventricular performance, as well as assessment of left ventricular performance from systolic time intervals, to elucidate these problems further. Both the echocardiographic measures of overall pump performance (percent shortening of left ventricular diameter and mean rate of circumferential shortening) and systolic time intervals have been shown to correlate well with measurements derived from invasive methods.[13–16] However, in patients with atrial septal defect the interventricular septal motion is usually abnormal and in some cases remains so even after closure of the defect. In these cases overall pump performance cannot be derived from the echocardiographically measured diameters and only an assessment of the regional performance of the ventricular wall is possible. Systolic time intervals, on the other hand, provide a measure of overall performance independent of any selective abnormality in motion of the left ventricular walls, and their use in conjunction with echocardiography is therefore particularly suited to the study of atrial septal defect.

In both groups in this study the echocardiographic measures showed no diminution in left ventricular systolic performance. The left ventricular posterior wall motion was even hyperdynamic in the group with an unrepaired defect compared with motion in the group with closed defect. In cases in which echocardiographic indexes of overall performance (percent shortening of left ventricular diameter and mean rate of circumferential shortening) could be measured, it was never diminished. These findings imply that there is no impaired contractility of the left ventricular myocardium in either group. However, systolic time intervals showed a statistically significant difference between the two groups, the group with an unrepaired defect (Group I) showing mean values consistent with mildly diminished performance by comparison with the more normal values in the group with a closed defect (Group II).

The difference in systolic time intervals between the two groups was accompanied by a significant difference in ventricular diameters. Group I showed not only the expected larger mean right ventricular diameter than Group II but also a smaller mean left ventricular diameter. Most of the patients in Group I had a left ventricular diameter below the mean normal value. This finding is in keeping with the observations of previous investigators[4,5,17,18] who found diminished left ventricular filling, volume and output in atrial septal defect. The small underfilled left ventricle would seem to be somehow related to the changes in the systolic intervals. This is implied by the finding of a significant correlation between the size of the shunt (and consequently the degree of underfilling of the left ventricle) and both the preejection period index (PEPI) and the PEP/LVET ratio. Furthermore, patients with abnormal systolic time intervals preoperatively showed prompt return of these measures to normal postoperatively concomitantly with prompt changes in the ventricular diameters (Fig. 5).

Explanation of changes in left ventricular diameters and performance: The changes in systolic time intervals might be explained by a direct effect of the underfilling of the left ventricle just as diminished preload of other causes is known to influence systolic time intervals.[12] However, it is questionable if the effect on systolic time intervals produced by acutely diminished preload is maintained in the chronic state. A possible alternate explanation is offered by recent studies[9,19,20] showing a major change in left ventricular geometric configuration and in the contraction sequence of the ventricular walls in atrial septal defect. Such a change, dependent on the coexistence of right ventricular volume overload in the presence of diminished left ventricular volume load, could explain a delayed rate of rise of left ventricular pressure during isovolumic systole with a consequent prolongation of the preejection period and shortening of the ejection time. This configurational change could also explain the presence of localized hyperactive posterior wall motion at a time when systolic time intervals indicate an overall diminution in left ventricular performance. The situation is similar to that in mitral regurgitation in which left ventricular wall motion is normal or hyperactive but systolic time intervals are mildly abnormal, possibly because the rate of pressure development in the ventricle is diminished as a result of loss of volume by ejection into the left atrium during the preejection period.[21]

Implications: Our findings indicate mildly diminished overall left ventricular performance in atrial septal defect, as demonstrated by systolic time intervals. This diminution occurs together with and appears to be somehow related to both volume overload of the right ventricle and concomitant diminished volume of the left

ventricle. However, there seems to be no impairment of myocardial contractility of the left ventricle, and after closure of the defect the size of the left ventricle and its performance return to normal. Longer follow-up studies with repeated noninvasive testing, perhaps coupled with stress testing, should be performed to elucidate further the possibility of latent left ventricular dysfunction not detectable in this study.

Acknowledgment

We thank Dr. Arnold M. Weissler for his review of the manuscript and helpful suggestions.

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Value of the QRS Complex in Assessing Left Ventricular Ejection Fraction

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The relation between electrocardiographic findings and the angiographic left ventricular ejection fraction and the augmented ejection fraction after a premature ventricular contraction was investigated in 73 patients with documented chronic coronary artery disease. The patients were separated into four groups according to the presence or absence of abnormal Q waves. Twenty-four patients had diaphragmatic myocardial infarction, 21 had anterior myocardial infarction, 15 had both and 13 had no myocardial infarction. There were no statistically significant differences in cardiac index, left ventricular end-diastolic pressure or number of coronary vessels showing critical narrowing in the four groups. The sum of R waves (in mv) in leads aVL, aVF and V_1 to V_6 (ΣR) was correlated with the ejection fraction (EF) and the augmented ejection fraction (EFa). EF in percent = 6.6 ΣR mv + 9.4 (no. = 73, r = 0.61); and EFa in percent = 8.6 ΣR mv + 11.0 (no. = 73, r = 0.77). Among patients with ΣR of less than 4.0 mv, augmented ejection fraction was less than 0.45 in 73 percent; among patients with ΣR of 4.0 mv or more the augmented ejection fraction was greater than 0.45 in 93 percent (P <0.001). Thus, the ΣR, calculated from six precordial and two augmented leads in patients with chronic coronary artery disease, correlated with both ejection fraction and augmented ejection fraction. The electrocardiogram in patients with coronary artery disease may prove useful as a simple, readily available and noninvasive guide in the assessment of left ventricular function in patients with coronary artery disease.

The left ventricular ejection fraction is among the most useful and readily obtainable measurements of left ventricular pump function[1–6] and provides important prognostic information concerning the outcome of medical and surgical therapy of patients with coronary artery disease.[5–9] The degree of augmentation of the left ventricular ejection fraction by catecholamines,[10] extrasystoles[7,11] or nitroglycerin[12] provides important additional information in patients with chronic coronary artery disease. Enhancing the contraction of viable contractile elements of the heart with these interventions unmasks the contractile reserve of the left ventricle.

Experimental studies[13,14] as well as clinical observations[15–17] have demonstrated a relation between changes in the QRS complex and the extent of myocardial infarction. In experimental animals the appearance of Q waves and the reduction of R wave height in epicardial leads correlate with necrosis in the myocardium subjacent to the epicardial electrode. A preliminary report[18] suggests that results of precordial mapping of Q waves in patients with acute anterior myocardial infarction correlate well with the extent of necrosis assessed with measurement of left ventricular dyskinesia and ejection fraction. The purpose of this study was to determine whether QRS changes in the standard resting electrocardiogram of patients with arteriographically documented

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TABLE I

Hemodynamic, Angiographic and Electrocardiographic Findings in 73 Patients With Coronary Artery Disease

Group	ECG	Patients (no.)	Average no. of Vessels Involved	LVEDP (mm Hg)	Cardiac Index (liters/min per m^2)	EF	EFa	ΣR
1	Normal	13	2.2 ±0.3	14.7 ±1.6	2.6 ±0.2	59.8 ±3.4‡	73.9 3.0‡	5.92 ±0.26*
2	DMI	24	2.6 ±0.2	15.2 ±0.1	2.5 ±0.1	38.4 ±2.4	52.7 ±2.4†	5.35 ±0.22†
3	AMI	21	2.4 ±0.2	18.0 ±2.0	2.4 ±0.1	34.4 ±2.3	42.5 ±2.6	3.72 ±0.21
4	AMI + DMI	15	2.8 ±0.2	17.6 ±1.7	2.5 ±0.2	31.7 ±2.0	41.8 ±2.1	3.63 ±0.22

* $P < 0.001$ between groups 1 and 3 and 1 and 4 but not significant between groups 1 and 2.
† $P < 0.01$ between groups 2 and 3 and groups 2 and 4.
‡ $P < 0.001$ between groups 1 and 2, 1 and 3 and 1 and 4.
AMI = anterior myocardial infarction; DMI = diaphragmatic myocardial infarction; ECG = electrocardiogram; EF = left ventricular ejection fraction, expressed as percent; EFa = augmented left ventricular ejection fraction after ventricular premature contraction, expressed as percent; LVEDP = left ventricular end-diastolic pressure; ΣR = sum of R wave voltage in eight leads (aVL, aVF and V_1 to V_6), expressed in mv.

coronary artery disease correlated with left ventricular ejection fraction measured both in the basal state and after an extrasystole.

Methods

Seventy-three patients (70 men and 3 women), with an average age of 52 years, who underwent right and left heart catheterization, left ventricular angiography and coronary arteriography for the evaluation of chest pain form the basis of this study.

Criteria for selection: Patients were included in the study if the following criteria were met: (1) A standard 12 lead scalar electrocardiogram, recorded on the morning before the study, showing normal sinus rhythm and no evidence of ventricular hypertrophy, intraventricular conduction delay, fascicular hemiblocks or true posterior myocardial infarction as defined by criteria set forth by the New York Heart Association.[19] (2) Arteriographic evidence of obstruction of more than 70 percent of the luminal diameter of at least one major coronary artery. (3) Ventriculogram showing opacification of the left ventricle before and immediately after a single premature ventricular contraction (induced or spontaneous). (4) Normal value of hematocrit (35 to 50 percent) because anemia or polycythemia may affect QRS amplitude.

Electrocardiographic evaluation: The patients were separated into four groups (Table I) according to the presence or absence of abnormal Q waves (duration of 40 msec or longer and amplitude of 0.2 mv or greater).

Group 1 (normal): Absence of abnormal Q waves.

Group 2 (anterior or lateral myocardial infarction, or both): Presence of abnormal Q waves in leads V_1 to V_6, I or aVL.[20]

Group 3 (diaphragmatic myocardial infarction): Presence of abnormal Q waves in leads II and III or aVF, or both.[20]

Group 4 (anterior and diaphragmatic myocardial infarction): Presence of abnormal Q wave satisfying the criteria for both anterior and diaphragmatic myocardial infarction, as defined for Groups 2 and 3.

The sum of R waves (ΣR) (expressed in mv) in leads aVL, aVF and V_1 to V_6 was calculated and *the number of abnormal Q waves* in the standard 12 lead electrocardiograms (except lead aVR) determined (Fig. 1). These two measurements were then correlated with the basal and augmented ejection fraction.

Cardiac catheterization and angiography: Catheterization studies included coronary arteriography with multiple views. Forty patients had left ventricular cineangiography performed in the 30° right anterior oblique projection and 33 patients had biplane left ventricular cineangiography in the 30° right anterior oblique and 60° left anterior oblique projections. Left ventriculography was carried out with a multihole angiographic catheter, using power injections of 30 to 50 ml of 76 percent meglumine and sodium diatrizoates over 3 to 4 seconds. After two or three normal sinus beats in which the ventricle was completely opacified, a single ventricular premature contraction was induced either electrically by using an R wave coupled stimulator (developed by the American Optical Company) and a bipolar catheter placed in the right ventricle,[11] or mechanically by moving the pacing catheter against the wall of the right ventricle, or spontaneously during the power injection. Quantitative ventriculography was carried out using a grid-calibration technique and left ventricular volumes were calculated by the area-length method of Dodge[21] and of Kasser and Kennedy.[22] The ejection fraction was calculated as the quotient of stroke volume and end-diastolic volume and expressed as percent. Cardiac output was determined using indocyanine dye or the Fick method. The left

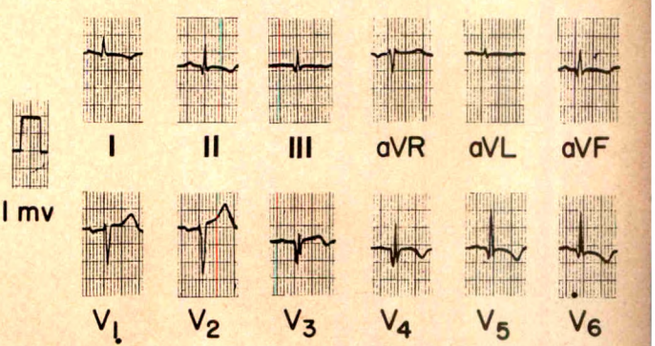

FIGURE 1. The electrocardiogram of a 54 year old patient showing old anterolateral and diagphragmatic myocardial infarction. The sum of R waves in aVL, aVF and V_1 to V_6 (ΣR) is 3.9 mv. The resting ejection fraction after a sinus beat was 0.29 and the augmented ejection fraction after a premature ventricular contraction was 0.49.

TABLE II

Relation Between Ejection Fraction (EF) and Augmented Ejection Fraction (EFa) and the Sum of R Waves (ΣR) in Eight Leads (aVL, aVF, V_1 to V_6)

		Cases (no.)	r	P
A. Ejection Fraction				
Total	= 6.6 ΣR mv + 9.4	73	0.61	<0.001
MI	= 4.2 ΣR mv + 17.2	60	0.49	<0.01
AMI	= 6.2 ΣR mv + 11.4	21	0.56	<0.01
DMI	= 5.4 ΣR mv + 9.7	24	0.49	<0.05
B. Augmented Ejection Fraction				
Total	= 8.6 ΣR mv + 11.0	73	0.77	<0.001
MI	= 6.8 ΣR mv + 16.5	60	0.77	<0.001
AMI	= 8.2 ΣR mv + 6.1	21	0.82	<0.001
DMI	= 5.0 ΣR mv + 25.9	24	0.60	<0.01

AMI = anterior myocardial infarction; DMI = diaphragmatic myocardial infarction; MI = myocardial infarction.

ventricular end-diastolic pressure was measured 60 msec after the onset of the QRS complex.

Statistical analyses were performed using Student's *t* test for independent observations and linear regression equations were calculated for each group.[23] All numerical results are expressed as mean ± standard error of the mean.

Results

The hemodynamic findings and the sum of R waves (ΣR) in the four groups are tabulated in Table I. There were no statistically significant differences in the number of vessels involved, left ventricular end-diastolic pressure or cardiac index among the four groups. The ejection fraction of the beat in sinus rhythm (EF) and the augmented ejection fraction (EFa) after a premature ventricular contraction were significantly higher in the group with coronary artery disease and normal electrocardiograms than in the groups with electrocardiographic signs of myocardial infarction ($P < 0.001$). There were no significant differences in ejection fraction among the three groups of patients with myocardial infarction, but the augmented ejection fraction was higher in patients with diaphragmatic myocardial infarction than in patients with anterior myocardial infarction or combined anterior and diaphragmatic myocardial infarction ($P < 0.01$) (Table I).

The relations between ΣR and both the ejection fraction and the augmented ejection fraction are summarized in Table II and plotted in Figure 2. The correlation coefficient between ΣR and the ejection fraction was 0.61 and between ΣR and the augmented ejection fraction was 0.77; the highest coefficient observed ($r = 0.82$) was between ΣR and the augmented ejection fraction in patients with anterior myocardial infarction.

In the 60 patients with abnormal Q waves, the number of abnormal Q waves in the 12 lead electrocardiogram showed little correlation with either the ejection fraction ($r = 0.19$, $P > 0.05$) or the augmented ejection fraction ($r = 0.36$, $P > 0.05$). When the number of abnormal Q waves was considered in addition to ΣR and related to ejection fraction and augmented ejection

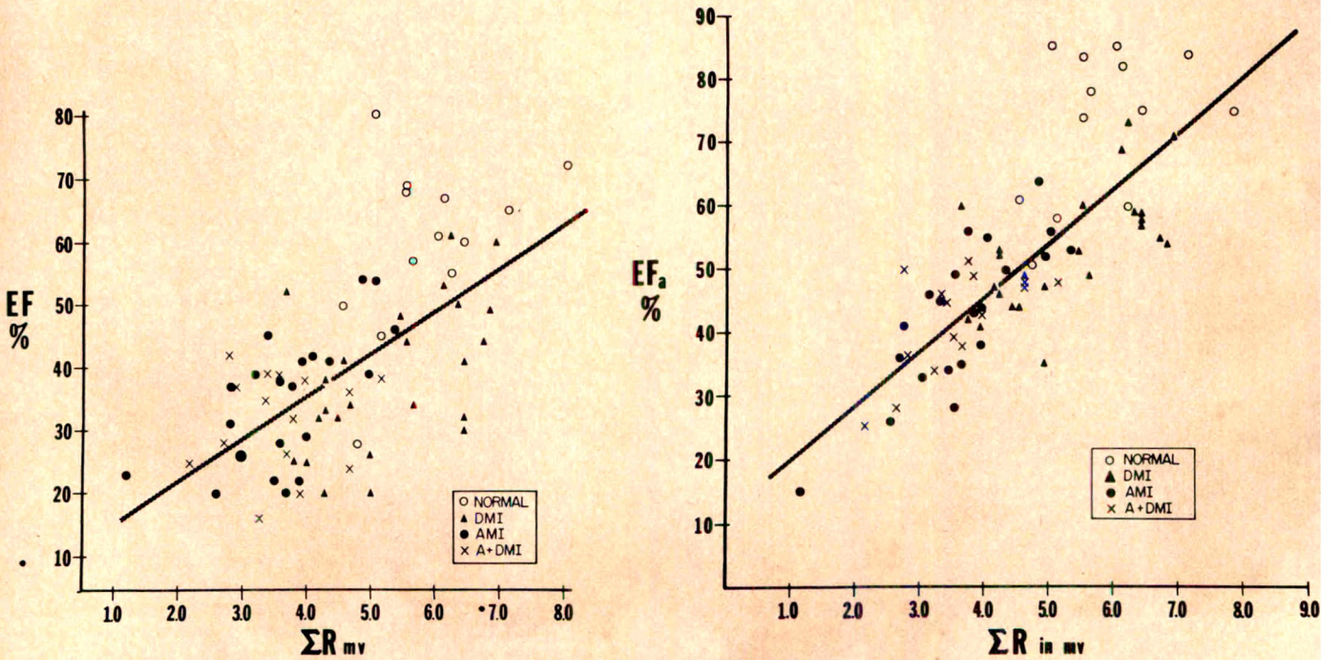

FIGURE 2. Left, relation between ejection fraction (EF) and the sum of R waves in eight leads (ΣR mv) (no. = 73, $r = 0.61$, $P < 0.001$). **Right,** relation between augmented ejection fraction (EF_a) and ΣR mv. Note the better correlation (no. = 73, $r = 0.77$, $P < 0.001$). AMI = anterior myocardial infarction; A + DMI = anterior and diaphragmatic myocardial infarction; DMI = diaphragmatic myocardial infarction.

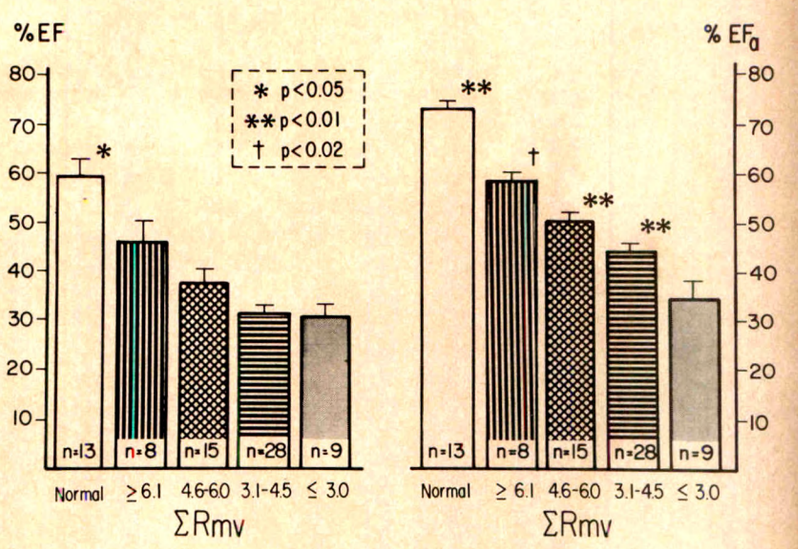

FIGURE 3. Left panel, relation between ejection fraction (EF) and ΣR in mv (ΣRmv) of eight unipolar leads in all 73 patients. The **shaded bars** represent four groups of patients with abnormal Q waves. The normal group represents patients with coronary artery disease but without abnormal Q waves. There was no significant difference in ΣR between the normal group and the group of eight patients whose ΣR was 6.1 mv or greater. **Right panel,** relation between augmented ejection fraction (EF_a) and ΣR mv in the same five groups. The **symbols** denote probability (p) values indicating differences in ejection fraction and augmented fractions of groups in **consecutive bars.** n = number of patients.

fraction, the correlation was not improved over that obtained with ΣR alone.

Relation among ΣR, Q waves and ejection fraction: The patients with abnormal Q waves were separated into four groups according to ΣR, and the findings were compared with those in patients with coronary artery disease but without abnormal Q waves (Fig. 3). The 13 patients without Q waves had an average ΣR of 5.9 ± 2.6 mv and their ejection fraction was significantly higher than that of the 8 patients with abnormal Q waves but comparable ΣR values. Among the four groups with abnormal Q waves the ejection fraction was significantly greater in the group with a ΣR value greater than 6.1 mv than in the groups with a ΣR value of less than 3.0 mv or 3.1 to 4.5 mv (P <0.01). ΣR was helpful in identifying patients with marked impairment of left ventricular performance. In the nine patients whose ΣR was less than 3.0 mv, the ejection fraction was abnormally low, averaging 0.316, and was never augmented by more than 0.10 after a premature contraction.

The classification of patients according to ΣR also allowed separation into groups in which the average augmented ejection fraction differed. A ΣR of 4.0 mv was useful in separating patients into those with and without moderately severe depressed left ventricular function; augmented ejection fraction was less than 0.45 in 22 of 30 patients (73 percent) whose ΣR was less than 4.0 mv but exceeded 0.45 in 40 of 43 patients (93 percent) whose ΣR was 4.0 mv or greater (P <0.001, chi square test).

Discussion

The ejection fraction has been identified as one of the most powerful predictors of survival in patients with coronary artery disease treated medically or surgically.[1,5–9,24,25] Recently, Dyke et al.[11] proposed a technique that measures contractile reserve by evaluating the augmented ejection fraction because basal values may be depressed for a variety of reasons including sedation, dye injection and ischemia. The method is based on determining the ejection fraction in the sinus beat following the ventricular premature contraction and comparing it with that of a sinus beat preceding the ventricular premature contraction. Patients with a depressed ejection fraction in the basal state who were able to increase their ejection fraction by more than 0.10 in the postpremature beat were considered to have reasonable contractile reserve and their prognosis appeared to be equal to that of patients with a higher ejection fraction. It also has been demonstrated that asynergic ventricular segments that show postextrasystolic improvement of contractility on left ventriculography have a normal uptake of thallium-201, whereas those that show no or little augmentation exhibit reduced uptake of the radionuclide. These observations suggest that the capacity of myocardium to improve contractile state signifies that it is perfused and viable, whereas inability to augment contractile state suggests that it is poorly perfused and perhaps necrotic.[26]

In classic experiments, Wilson and his collaborators[27,28] described the changes in the QRS complex recorded from the epicardium in the presence of myocardial infarction and postulated that a QS wave resulted from the transmission of negative cavity potential through necrotic myocardium. Prinzmetal and his coworkers[29,30] confirmed this theory of the genesis of Q waves in infarction but pointed out that in some instances a QS complex may result from a balance of vectors directed away from the injured site in the absence of through and through infarction. In experimental studies on the origin of QR waves, Shaw et al.[13] emphasized that viable myocardium must be present in subjacent tissue for R waves to appear. A number of studies have suggested a correlation between electrocardiographic changes and myocardial infarct size[16–18] as well as with hemodynamic findings.[18,31] In patients with coronary artery disease an electrocardiographic "score" based on the severity of electrical abnormalities

was found to be a better predictor of ejection fraction than other noninvasive modalities, such as the chest roentgenogram, systolic time intervals and echocardiogram.[32]

In this study of patients with angiographically documented coronary artery disease, the sum of amplitudes of R waves in eight unipolar leads (ΣR) was related to the left ventricular ejection fraction and the augmented ejection fraction. ΣR correlated better ($r = 0.77$) with the latter than with the basal ejection fraction. The best correlation ($r = 0.82$) occurred in patients with old anterior myocardial infarction and the poorest ($r = 0.60$) in the patients with old diaphragmatic myocardial infarction; this difference may have resulted from the fact that the anterior and lateral aspects of the left ventricle are "viewed" by six precordial leads (V_1 to V_6) and one augmented lead (aVL), whereas the diaphragmatic aspect of the myocardium is represented by only a single lead (aVF) and is therefore "underweighted" in the calculations of ΣR. Nevertheless the standard electrocardiogram appears to be valuable in reflecting augmented ejection fraction in patients with old anterior and lateral wall infarction.

Our results indicate that a higher ΣR is associated with a higher ejection fraction and augmented ejection fraction in patients with old myocardial infarction. Thus, the findings are consistent with experimental observations that viable myocardium is represented by epicardial R waves. The patients with coronary artery disease but without abnormal Q waves constitute a separate group in which the augmented ejection fraction was generally normal and there was little correlation between ΣR and the augmented ejection fraction in this group. In patients with electrocardiographic evidence of old myocardial infarction, as defined by the presence of abnormal Q waves but a ΣR of 6.1 mv or more, both the ejection fraction and the augmented ejection fraction were significantly lower than in the patients without abnormal Q waves who had comparable value of ΣR. An ejection fraction of 0.45 has been suggested as a cutoff point for identifying moderately severe impairment of ejection fraction[33]; ΣR of 4.0 mv served as a valuable guide because it was helpful in separating patients with an augmented ejection fraction above and below 0.45. These cutoff levels now need to be tested in a new group of patients.

Implications: The resting standard 12 lead electrocardiogram contains more information concerning left ventricular contraction in patients with coronary artery disease than is generally recognized. Our findings suggest that the sum of R waves in eight unipolar limb and chest leads (ΣR) correlates well with the left ventricular ejection fraction and augmented ejection fraction and may prove to be a useful noninvasive guide in the evaluation of patients with coronary artery disease.

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Atrioventricular Block: Natural History After Permanent Ventricular Pacing

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The preimplantation status, postimplantation morbidity and causes of late mortality were summarized for 246 patients who underwent pacing for atrioventricular (A-V) block at the University of Michigan for the 14 years from 1961 to 1974. The survival rate at 1, 5 and 10 years was 88, 61 and 49 percent, respectively. Risk of death was greatest among patients with antecedent ischemic or hypertensive heart disease or congestive heart failure in the period before pacemaker implantation, patients older than 74 years at initial implantation and those receiving a pacemaker before 1965. Forty-two percent of the 109 deaths were related to apparent progression of underlying cardiac disease. Pacing system malfunction was a contributing documented cause of only 3 deaths. Even with permanent pacemaker implantation, patients with A-V block have a higher age-specific mortality rate than the general U.S. population. Survival improved steadily over the period of study. This change is attributed to apparent improvements in treatment of cardiovascular disease including more effective treatment of congestive heart failure and valve replacement for selected patients as well as elimination of immediate postoperative mortality.

Permanent ventricular pacing has been the recognized treatment for atrioventricular (A-V) block for more than 15 years. Previous reports[1–4] have documented the continued morbidity and mortality in patients with A-V block who have received pacemakers. This report reviews the status of such patients to determine the natural history of this disorder after permanent pacemaker implantation, the causes of late morbidity and mortality and the changes in mortality that occurred during the follow-up period. Survival of this population group was also compared with that of the U.S. population matched for age, race and sex.

Methods

The records of all adult patients who received permanent pacemakers at the University of Michigan Medical Center from 1961 through 1974 were reviewed. Many of the patients have been the subject of previous reports from this institution.[4–11] Since 1965, all patients have been followed up in a pacemaker clinic. Data on the history, clinical course, specific arrhythmias seen and follow-up findings were transferred to computer tape. Survival curves were determined with the life table method[12,13] utilizing the Michigan Interactive Data Analysis System (MIDAS)[14] and the Interactive Graphic Survival Analysis System (IGSAS).[15] For each patient survival time was calculated from the date of the first pacemaker implantation until death or the end of the observation period, March 1, 1976. For the one patient who was lost to follow-up, survival was calculated from the date of implantation to the date of last follow-up.

Patient selection: The study population consisted of 246 adult patients who received their initial pacemaker at the University of Michigan Medical Center for an A-V conduction disturbance during the years specified. Patients with bifascicular block and syncope, but without documentation of complete A-V block, and two patients with atrial fibrillation and advanced second degree block

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were also included. Fifty-seven patients who underwent pacing for sinus node disease, hypersensitive carotid sinus syndrome or drug-resistant ventricular tachycardia, 20 patients in the pediatric age group (14 years or less) and 19 patients who received their initial pacemaker elsewhere were excluded.

Derivation of survival data: The Breslow's generalized Kruskal-Wallis Test was utilized to determine if the survival distribution differed across strata for any single preimplantation variable.[16] The survival data for the "control" U.S. population were derived from abridged life tables for race and sex found in reports of the vital statistics of the United States from 1962 to 1973.[17,18] Each individual study patient was matched to a life table specific to year of initial implantation, sex and race. A t statistic was then computed to test the null hypothesis that the mean of the differences between the survival times of the patients and control subjects was zero. This was computed for the entire population and for each age stratum used (less than 65, 65 to 74 and more than 74 years).

Classification of heart disease: The etiology of the heart disease associated with the conduction disturbance was inferred from the available clinical data. Arteriosclerosis was accepted as a cause of disease only if the patient had a myocardial infarction documented by enzyme or electrocardiographic criteria or definite angina pectoris. Rheumatic heart disease was considered a cause if the patient had cardiac valve disease, usually of both the aortic and the mitral valves, a positive history of acute rheumatic fever or pathologic evidence of it at the time of operation or autopsy. Isolated aortic valve disease was considered a cause when appropriate physical findings were accompanied by a negative history for rheumatic fever and no pathologic changes of rheumatic heart disease at operation or autopsy were found. Patients with a faint systolic ejection murmur alone were not classified in this category. Patients with calcific aortic stenosis and idiopathic aortic insufficiency, as well as those with aortic valve disease secondary to other disease processes (for example, ankylosing spondylitis), were included in this category. Patients were judged to have cardiomyopathy if they had severe generalized cardiomegaly with or without congestive heart failure before pacing and if no other apparent cause for the cardiomegaly was evident. Congenital heart disease was diagnosed on the basis of the usual clinical, cardiac catheterization and surgical criteria. Hypertensive heart disease was defined as radiographic cardiomegaly or evidence of left ventricular hypertrophy in the electrocardiogram combined with repeated recordings of blood pressure greater than 160/90 mm Hg.

When a patient had more than one form of heart disease, the apparent dominant etiology at the time of initial implantation was utilized for classification purposes. Patients whose condition did not satisfy the criteria for any of the categories cited were classified under "idiopathic." Patients in this category were free of hypertension, had no antecedent myocardial infarction or angina pectoris, had no significant murmurs and had a normal heart size or only slight cardiomegaly without congestive heart failure at implantation.

Determination of cause of death: The method for determining the cause of death was similar to that previously described.[19] Details concerning the circumstances of death were obtained by interviewing the patient's physician, family members or other informed witnesses. Hospital, autopsy and medical examiner records and terminal electrocardiograms were obtained whenever feasible. Available pacing system components were retrieved for electronic analysis after death whenever possible.

Sudden death was defined as death within 1 hour of the onset of symptoms[20]; for most of the patients included here, death was apparently instantaneous or nearly so. Definite congestive heart failure was diagnosed on the basis of examination of available records and utilization of the criteria of McKee et al.[21] Two or more of the following signs and symptoms were required: exertional dyspnea, paroxysmal nocturnal dyspnea, neck vein distension, cardiomegaly, rales, pulmonary edema, third sound gallop or positive hepatojugular reflux or weight loss of 4.5 kg or more in response to treatment. The minor criteria of McKee were not utilized.

Type of pacemaker implant: From 1961 to 1965, every patient received an epicardial lead implant through a left or anterior thoracotomy under general anesthesia. Since 1965

TABLE I

Major Symptomatic Disease States Before Initial Pacemaker Implantation Correlated With Year of Implantation*

Diagnosis	1961–64 (no. = 51) no.	%	1965–69 (no. = 103) no.	%	1970–74 (no. = 92) no.	%	Total (no. = 246) no.	%	P Value
Cardiovascular									
Angina pectoris	4	7.8	10	9.7	15	16.3	29	11.8	
Myocardial infarction	6	11.8	11	10.7	25	27.2	42	17.1	<0.005
Congestive failure	17	33.3	36	35.0	35	38.0	88	35.8	
Systolic hypertension	22	43.1	54	52.4	51	56.0	127	51.8	
Diastolic hypertension	11	21.6	12	11.7	19	20.9	42	17.1	
Peripheral (arterial) vascular disease	4	7.8	12	11.7	9	9.8	25	10.2	
Cerebrovascular disease (including transient ischemic attacks, stroke, embolism, subdural hemorrhage, organic brain syndrome)	5	9.8	10	9.7	17	18.5	32	13.0	
Syncope	43	84.3	81	78.6	50	54.3	174	70.7	<0.001
Cardiomegaly (definite)	23	46.9	47	46.1	38	41.3	108	44.4	
Other									
Diabetes mellitus	12	23.5	27	26.2	19	20.7	58	23.7	
Renal disease	12	22.5	18	17.5	26	28.3	56	22.8	
Obesity	10	19.6	27	26.2	38	41.3	75	30.3	<0.025
Obstructive lung disease	5	9.8	17	16.5	10	10.9	32	13.0	
Cancer	4	7.8	11	10.7	8	8.7	23	9.3	

* There is no significant difference over the 14 year period of the study as to patient selection except as specified. Most patients had multiple conditions.

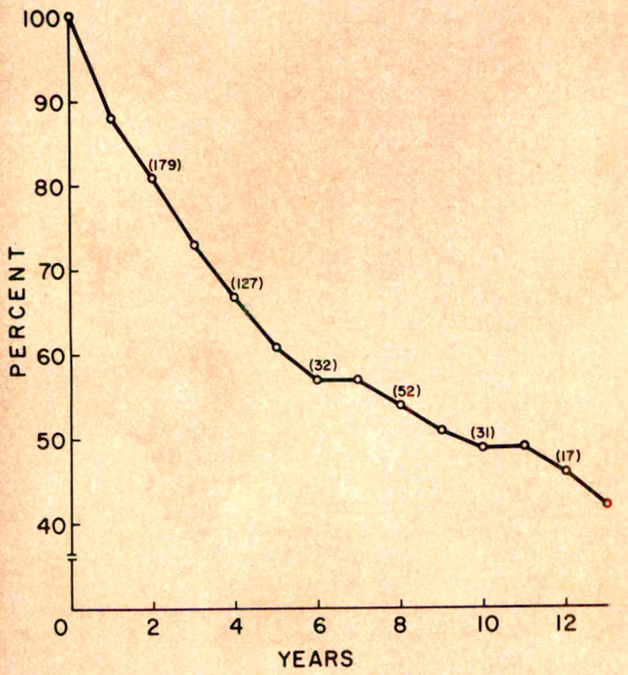

FIGURE 1. Survival after initial pacemaker implantation. The numbers in parentheses beside each 2 year point signify the number of patients remaining at each interval.

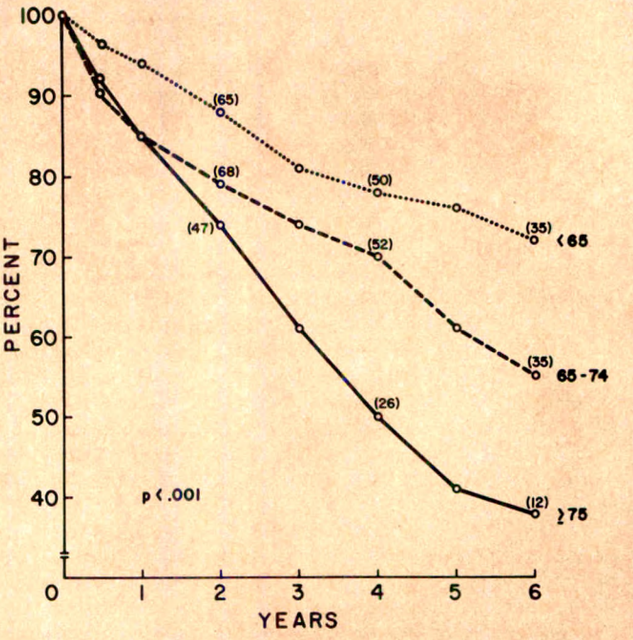

FIGURE 2. Survival after initial pacemaker implantation correlated with age at entry. Age as a predictor of mortality was highly significant, but when analyzed separately patients in the intermediate age range were not significantly different from the very elderly ($P = 0.15$).

two thirds of the patients have had the transvenous approach as the implantation method of choice. During the follow-up period pacing was performed with General Electric, Medtronic, Cordis or CPI pacing systems. Patients received from 1 to 12 pulse generators during the follow-up period.

Results

The 246 adult patients who received a permanent ventricular pacemaker for A-V heart block consisted of 159 men and 87 women; only 8 were nonwhite. The mean age at initial implantation was 66 years (range 16 to 89); 27 percent were 75 years of age or older and 35 percent were less than 65 years.

Before pacemaker implantation, these patients had a large prevalence of symptomatic cardiovascular disease and other illnesses as well (Table I). Diabetes mellitus was present in 24 percent and symptomatic chronic obstructive lung disease in 13 percent; 9 percent had a history of major organ malignant neoplasm and 30 percent were obese. A prior myocardial infarction could be documented in only 17 percent; congestive heart failure was present in 36 percent. Transient cerebral ischemic attacks, previous stroke and arteriosclerotic peripheral vascular disease were also common. With the exception of obesity, there was no significant difference in prevalence of any chronic disease state in patients selected for pacing over the period of the study (Table I).

TABLE II

Survival of Paced Population Over the Time of the Follow-up Period Compared With Survival of Age-Sex-Race–Matched Control Subjects from the U.S. Population

Age (yr)	Patients (no.)	Observed Survival (mo)	Expected Survival (mo)	*P* Value
<65	86	70	83	<0.002
64–74	93	57	73	<0.002
≥75	67	45	59	<0.002
All ages	246	58	73	<0.0001

Survival

The survival rate of the entire group was 61 percent at 5 years and 49 percent at 10 years. The highest mortality rate (12 percent) occurred in the first year (Fig. 1). Survival was highly correlated with age at initial implantation (Fig. 2). Patients under age 65 had a 5 year survival rate of 75 percent, whereas only 40 percent of those over age 74 lived more than 5 years. Patients in the intermediate age group (65 to 74 years) had a 5 year survivorship of 61 percent ($P = 0.002$). For each age group the patients with pacing had a shorter survival time than the general population (Table II). Mean survival time for all patients with pacing was 58 months compared with an expected survival time of 73 months ($P < 0.001$).

Mortality and year of initial implantation: Mortality also correlated with the year of initial implantation. In Figure 3 the study group is divided into three subgroups stratified by the year of initial pacemaker implantation—1961 to 1964, 1965 to 1969 and 1970 to 1974. Survival improved progressively in each interval,

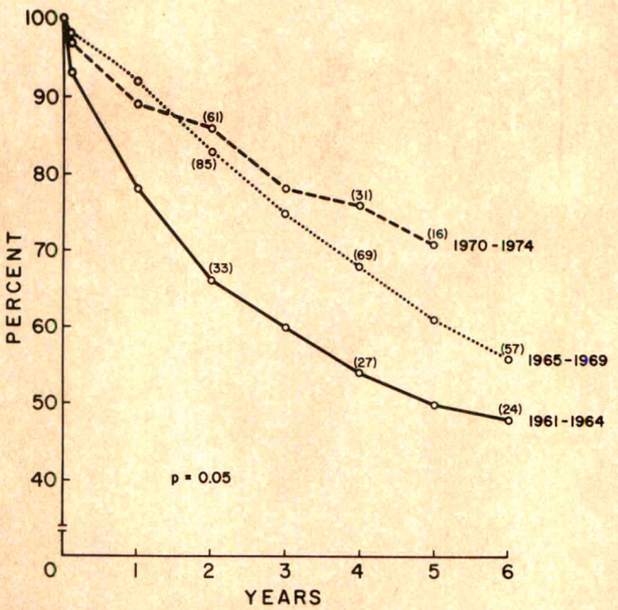

FIGURE 3. Survival after implantation correlated with year of implantation. The excessive first year mortality in the 1961 to 1964 period is due in part to perioperative mortality associated with epicardial implants used exclusively in that time period. When analyzed separately, the 1965 to 1969 group did not differ significantly from the 1970 to 1974 group ($P < 0.20$).

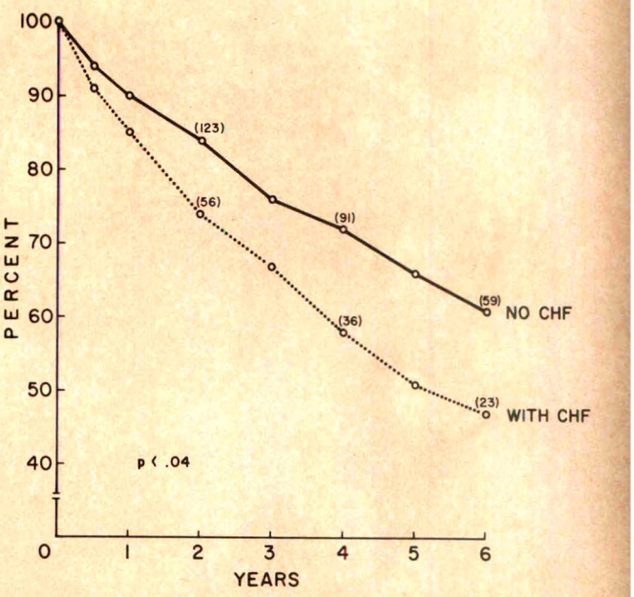

FIGURE 4. Survival after initial pacemaker implantation correlated with the presence of congestive heart failure (CHF) before implantation.

with 5 year survival rates of 50, 61 and 71 percent, respectively, for the three intervals specified ($P < 0.05$). The high mortality rate in the first year in the 1961 to 1964 period is explained in part by the 8 percent perioperative mortality rate (4 of 51 patients) associated with the transthoracic epicardial operative approach available at the time. An additional patient died during a second epicardial implantation within the first year. No patient in this series died postoperatively when the transvenous approach was used.*

Mortality related to congestive failure and type of heart disease: The presence of congestive failure in the preimplantation period was also predictive of a higher mortality rate (Fig. 4). Those with definite heart failure in the preimplantation period had a survival rate of 73 and 49 percent at 2 and 5 years, respectively, whereas those free of congestive heart failure had a survival rate of 87 and 69 percent at these time intervals ($P < 0.04$). Other medical conditions did not, as independent variables, appear to affect survival significantly, except for those patients with a preimplantation diagnosis of malignant neoplasm ($P < 0.001$). Patients with systolic or diastolic hypertension and cerebrovascular disease had an insignificantly increased risk of death; the presence of diabetes mellitus, obesity, chronic obstructive lung disease, hyperlipidemia, chronic renal disease or peripheral vascular disease did not increase the rate of late mortality.

The etiology of underlying heart disease did correlate with a greater late mortality (Fig. 5). Patients with ischemic or hypertensive heart disease had the poorest survival rate, only 40 percent living beyond 60 months. The 111 patients (45.5 percent) with "idiopathic" disease did far better; 87 and 72 percent survived 24 and 60 months, respectively. Patients with isolated aortic valve disease and rheumatic heart disease had an intermediate survival rate. There were two deaths by 42 months in the small group of seven patients with congenital heart disease, six of whom had iatrogenic complete heart block. Ten patients with apparent primary myocardial disease had a survival rate similar to that of the group with aortic valve disease. The relation between the etiology of underlying clinical heart disease and survival was highly significant ($P < 0.002$).

By combining variables it is possible, retrospectively, to group the patient population into those with a high (more than 85 percent) and very low (less than 25 percent) probability of survival at 5 years. Patients in the first category were less than 65 years old at initial implantation and had no history of myocardial infarction or congestive heart failure. Patients in the highest risk group were more than 74 years old, and had both angina pectoris and myocardial infarction before the initial implantation.

Morbidity and Causes of Late Mortality

Morbidity: During the course of follow-up, new major cardiovascular events were common. Twenty patients (9 percent) had an acute myocardial infarction, and 27 (11 percent) manifested congestive heart failure that had not been present before implantation. Central nervous system events (transient ischemic attacks,

* At this institution in the same time period one patient with permanent pacing for sinus node disease died of an acute myocardial infarction and two patients with pacing for drug-refractory ventricular tachycardia died of recurrent arrhythmias within 14 days of transvenous pacemaker implantation; these patients were not included in our analysis because their indication for pacing was not A-V block.

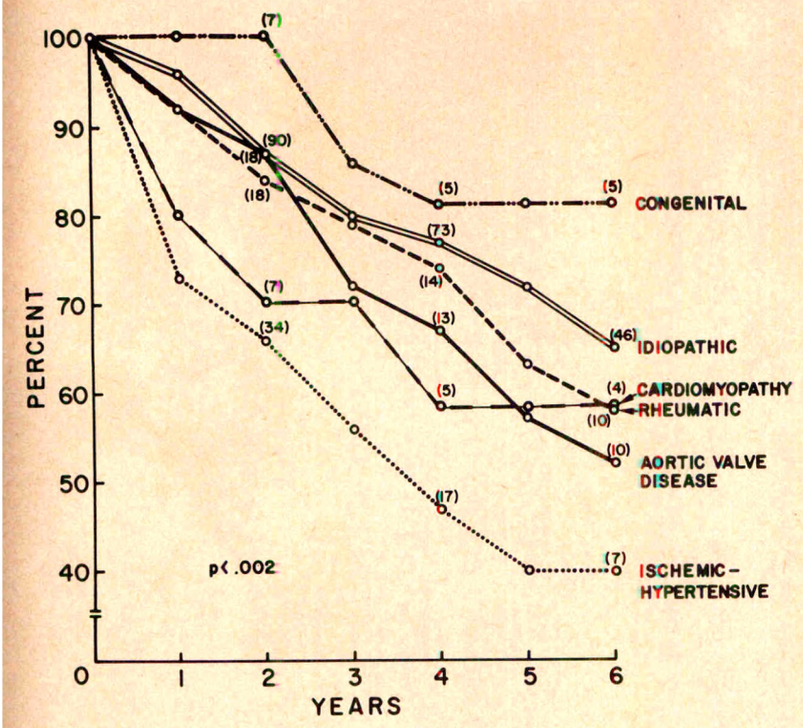

FIGURE 5. Correlation between survival and clinically apparent etiology of heart disease. Patients with ischemic-hypertensive disease did least well, 27 percent dying in the first year.

completed stroke or progressive organic brain syndrome) were noted in 35 patients, and in 12 percent stroke was the primary cause of death (Table III). In addition, 19 patients (8 percent) had progressive azotemia, 15 had a new malignancy and 24 (10 percent) had a major pulmonary event (pneumonia, pulmonary insufficiency or embolism).

Causes of death: Forty-two percent of patients died of apparent cardiac causes (Table III); over half of these died suddenly (in 1 hour or less). Six percent died of definite or probable myocardial infarction. There was no correlation between the mode of death in those patients paced with asynchronous (VOO) versus synchronous (VVI) pulse generators at death, or in those from any time period.

TABLE III

Causes of Death During Study Interval

	no.	Percent*
Cardiac	46	42
Sudden death (<1 hour)	24	20
Congestive heart failure	15	14
Myocardial infarction	6	6
Refractory ventricular tachycardia	2	2
Noncardiac	34	31
Central nervous system	13	12
Cancer	9	8
Other (infection, pulmonary embolism, pneumonia, uremia, etc.)	12	11
Unknown (unwitnessed, unspecified, unavailable data)	21	19
Pacemaker failure	3	2
Perioperative	5	5
Total	109	100

* Expressed as percent of all deaths.

The exact cause of death could not be established in 19 percent. Patients in this category frequently died with multiple illnesses in convalescent facilities and clinical data were not sufficient for accurate classification. Many of these patients were found dead, and no autopsy or medical examiner reports were available. From the limited information available on these latter patients, symptomatic cardiovascular disease appeared to be the most plausible cause of death in most instances. Autopsy and pulse generator inspection data were obtained in 21 percent of the 109 fatal cases; 36 percent of the patients died in a hospital, and 13 percent in a nursing or convalescent facility. Death was related to pacing unit malfunction in at least three patients. One patient died with pulmonary edema and the terminal electrocardiogram documented failure to capture and slow idioventricular rhythm. One patient died suddenly and the returned pulse generator had no output. Sudden death was associated with battery depletion in the third.

Discussion

Contribution of permanent cardiac pacing to increased survival of patients with A-V block: Several studies are available on the "natural history" of A-V block before the era of permanent pacing.[22–30] Although the case selection and follow-up methods in these studies differ considerably, the frequently quoted mortality rate of approximately 50 percent within the first year after the diagnosis of complete A-V block seems reasonably accurate. Johansson[25] called attention to the variations in mortality in the prepacing era in relation to age at onset and clinical setting of A-V block. Differences in patient population, improvements in care

TABLE IV

Specific Arrhythmias Noted at Time of Initial Implantation and Other Descriptors of the Population Correlated With Year of Implantation*

	1961–64 no. = 51		1965–69 no. = 103		1970–74 no. = 92		Total no. = 246		*P* Value
	no.	%	no.	%	no.	%	no.	%	
Complete A-V block	42	82.4	83	80.6	73	79.3	198	80.5	<0.001
Intermittent complete heart block	8	19.0†	25	30.1†	41	56.1†	74	37.4	
Permanent	34	81.0	58	69.9	32	43.8	124	62.6	
Second degree A-V block	8	15.7	21	20.4	19	20.6	48	19.5	
Type I					5	5.3	5	2.0	
Type II	2	3.9	6	5.8	5	5.3	13	5.3	
2:1 block only	6	11.8	15	14.6	9	10.0	30	12.2	
Premature ventricular beats	11	22.0	27	26.2	28	30.2	66	26.8	
Ventricular tachycardia or cardiac arrest	5	9.8	8	7.8	6	6.5	19	7.7	
Duration of heart disease (mean yr)	6.1		5.5		4.9				
Duration of intraventricular conduction defect (mean yr)	3.1		2.0		1.3				
Duration of A-V block (mean yr)	1.8		1.0		0.9				

* Patients in the earlier years had symptomatic heart disease for a longer period of time than those selected later and had a higher frequency of permanent complete A-V block.

† Expressed as a percent of those with complete A-V block.

TABLE V

Etiology of Underlying Heart Disease at Entry as Correlated With Year of Initial Implantation*

	1961–64 (no. = 51)		1965–69 (no. = 103)		1970–74 (no. = 92)		Total (no. = 246)	
	no.	%	no.	%	no.	%	no.	%
Idiopathic	24	47.1	53	51.5	36	39.1	113	45.9
Ischemic-hypertensive	12	23.5	18	17.5	37	40.2	67	27.2
Rheumatic	8	15.7	9	8.7	8	8.7	25	10.2
Cardiomyopathy	1	2.0	5	4.9	4	4.3	10	4.1
Aortic valve disease	2	3.9	15	14.6	7	7.6	24	9.8
Congenital	4	7.8	3	2.9	—	—	7	2.8

* See text for definitions. Six of the seven patients with congenital heart disease have iatrogenic complete heart block.

of congestive heart failure and other medical problems, the introduction of palliative operative procedures for congenital and valvular heart disease as well as improved methods of diagnosis (possibly, therefore, including patients at an earlier stage of their disease) prevent accurate comparison between patients with symptomatic advanced second degree or complete A-V block now treated with permanent pacing and "control" subjects observed in the 1940 to 1960 period. Even after these limitations are acknowledged, the improvement in survival in current series is so dramatic that there is little doubt that pacing has drastically increased survival of patients with this arrhythmia.

Nevertheless, patients with permanent pacemakers implanted for A-V block do continue to experience cardiovascular morbidity and mortality and have a significantly higher mortality rate than the general U.S. population. Although patients with conduction disturbances are found in every age group, this population is, in general, an elderly group with a high prevalence rate of chronic diseases including malignant neoplasm, obstructive lung disease, diabetes mellitus, peripheral and cerebrovascular disease and renal failure. Progression of cardiovascular disease, including recurrent or new congestive failure, myocardial infarction and stroke as well as sudden death, account for over half and probably three quarters of all late deaths in these patients. In addition, age, antecedent ischemic heart disease and congestive heart failure before permanent pacing are important predictive factors for early mortality after successful pacemaker implantation. It is unlikely that differences in patient selection played a significant role in the higher patient mortality rate in the early time period (Table IV). Although patients in the 1961 to 1964 period had a greater prevalence of syncope, fixed complete A-V block and a slightly longer duration of symptoms than those patients in the later periods, their age and the prevalence rate of congestive heart failure, angina pectoris and prior myocardial infarction were no higher (Table I). For example, 35 percent of the patients in the earlier time period had A-V block or syncope for more than 1 year, whereas only 20 percent of those in the last time period had symptoms of that duration. In fact, the prevalence of ischemic heart disease and congestive heart failure was slightly greater in the later years (Tables IV and V), perhaps

reflecting a trend toward the use of pacing in patients who might have been excluded in the earlier time period because of the need for a general anesthetic and thoracotomy. Elimination of perioperative mortality associated with general anesthesia as well as improved medical and surgical methods of treatment of cardiovascular disease have probably contributed to this improvement in survival.

Role of pacemaker failure in late deaths: Between 1961 and 1967 all pacing was performed with asynchronous (VOO)[31] pulse generators whose reliability and longevity were inferior to those of currently available models.[10] Pacing system failure appeared to contribute to very few deaths in previously reported series.[1,32–39] In our group sudden death was no more common in the early period and was not more common in patients paced with asynchronous (VOO) units. Because unwitnessed death[16,17] and deaths due to unknown causes constitute a relatively large part (19 percent in our series) of all deaths in patients undergoing pacing and because the pulse generator and pacing lead could be inspected in only a few of those who died suddenly, some uncertainty must remain concerning the role of the pacing system in these deaths. This question can be resolved only by a systematic complete examination of a selected group of pacing systems after death in patients who die suddenly or of unknown causes.

Mortality findings in our series are similar to those previously reported by others.[1–3,32–39] The somewhat better overall survival rate compared with that of some other series may be attributed to a slightly younger patient population, a lesser prevalence of prior acute myocardial infarction and the later period from which the patients were drawn. As in other studies, mortality appears to be greatest in the first year after the initial pacemaker implantation.

Role of congestive failure in early mortality and indication for sequential atrial pacing: Congestive heart failure as a predictor of earlier patient death deserves special mention. Numerous studies have documented improved hemodynamics and disappearance of signs and symptoms of congestive failure after permanent pacing.[40] However, persistent cardiomegaly,[25] continued dependence on digitalis and diuretic agents, and the failure of permanent pacemaker implantation to alleviate congestive heart failure in some patients is well documented.[41] Recurrent or new heart failure was common in our series. The rate of death was significantly greater for patients with definite congestive heart failure before implantation and, in fact, the mortality rate of patients with congestive heart failure and A-V block after pacing in our series closely approximates that of the Framingham study patients with heart failure without A-V block.[21] Heart failure that accompanies A-V block is often only partially due to the slow rate itself, and impaired ventricular function in patients after permanent ventricular pacing is not uncommon. There may be a distinct role for A-V synchronous (VAT) or sequential pacing (DVI) in patients with maintained atrial function in order to take full advantage of the atrial contribution to cardiac output in patients with A-V block. Studies by Leinbach et al.[42] and others have shown a 20 percent improvement in resting cardiac output with this mode of pacing compared with ventricular pacing alone. The development of improved transvenous atrial electrodes will be necessary to test the possibility of whether such pacing will be beneficial to enough patients to warrant its widespread use in those with persistent or severe congestive failure and A-V block.

Implications: In our study sudden death was the most common mode of death in the population undergoing pacing for A-V block. Preliminary data indicate that ventricular arrhythmias of a serious nature are common in such patients (unpublished data). However, at this juncture there is little evidence to indicate that available antiarrhythmic agents decrease the frequency of complex ventricular arrhythmias consistently in this population or that they will decrease the incidence of late sudden death.

Several longitudinal studies have demonstrated that patients undergoing pacing for A-V block and probably for sinus node disease as well[43,44] have a high mortality rate in the first 5 years after initial pacemaker implantation. Certain groups of these patients appear to have an especially poor survival rate, including those with impaired left ventricular function before implantation, those over age 74 at initial implantation and those with a prior history of ischemic heart disease.

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Thromboembolism in Mitral Porcine Valve Recipients

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A low incidence rate of thromboembolism has been reported in mitral porcine valve recipients. In contrast, 5 of 22 single mitral porcine valve recipients (23 percent) followed up in our clinic for a mean of 16 months had thromboembolic events. All patients but one were receiving long-term anticoagulant therapy. One thromboembolic event resulted in death, three in permanent neurologic deficits and one in a peripheral arterial occlusion. All five patients with emboli had atrial fibrillation and left atrial enlargement. Three had thromboembolic events before porcine heart valve implantation. In addition, five mitral porcine valve recipients who were not receiving anticoagulant therapy were examined at autopsy. Thrombus was identified in the left atrium in three patients, at the tissue-valve interface (sewing ring) in two, on the porcine valve cusps in one and in the right atrium in one.

Factors influencing thrombus formation such as left atrial enlargement, atrial fibrillation and a prosthetic device are present after mitral porcine valve implantation and are indications for long-term anticoagulation therapy.

Thromboembolism is a major source of morbidity and mortality in patients with severe mitral valve disease, especially when atrial fibrillation, enlarged left atrium and decreased cardiac output are present.[1,2] Although mitral valve replacement with a rigid prosthesis usually results in hemodynamic improvement, the problem of thromboembolism remains.[3,4] Reports of reduced thromboembolism after mitral porcine valve implantation have been encouraging;[5–9] however, continued critical review of patient and autopsy findings is needed. This report reviews our clinical and autopsy experience with mitral porcine valve recipients. The incidence of thromboembolism in our patients is compared with reported data.

Study Groups

Clinic patients: Twenty-two patients received a Hancock mitral valve prosthesis as a single valve replacement at the Los Angeles County-University of Southern California Medical Center from September 1974 through January 1977. There were no operative deaths. Ten patients were men, and 12 were women. The mean age was 46 years (range 23 to 64 years). The cause of the mitral valve disease was rheumatic heart disease in 17, idiopathic ruptured chordae tendineae in 4 and acute bacterial endocarditis in 1. Two patients had previously received a Kay-Shiley mitral valve prosthesis. The predominant rhythm was atrial fibrillation in 18 patients, regular sinus in 3 and nodal in 1. All patients had left atrial enlargement on echocardiographic examination or chest X-ray, or both. Three patients were in New York Heart Association functional class IV preoperatively, 12 in class III, 6 in class II and 2 in class I.[10] Except for those in class IV, the functional class was determined in each using maximal effort exercise testing with the Bruce protocol.[11]

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TABLE I

Thromboembolic Events in Recipients of a Single Mitral Porcine Heart Valve

Patient no.	Age (yr)	Duration Postop	NYHA Class*	Prothrombin Activity* (%)	Clinical Presentation	Previous Thromboembolic Events
1	39	10 days	II	26	Transient aphasia, slurred speech	3 similar episodes before operation
2	62	4 mo	III	52	Right hemiparesis, intracranial hematoma and death	Left hemiparesis 2 years before operation
3	23	8 mo	II	30	Right brachial artery occlusion, surgically removed	Anterior myocardial infarction
4	60	9 mo	III	11	Transient right hemiparesis, generalized seizures, permanent VII nerve paresis	None
5	33	18 mo	II	115	Transient right paresis and permanent right homonomous hemianopsia	None

* At time of hospitalization for thromboembolic event.
NYHA Class = New York Heart Association functional class[10]; TE = thromboembolic.

After discharge from the hospital, all patients were followed up by the same group of physicians, nurses and clinical pharmacists in the prosthetic valve clinic at the medical center. The total follow-up period for the 22 patients referred to the clinic was 345 patient months, with a mean follow-up period of 16 months. All patients were prescribed oral warfarin therapy in an attempt to maintain prothrombin activity between 10 and 20 percent.[12] Neither aspirin nor dipyridamole was employed. Return visits were scheduled on a 1 to 3 week basis, and strict attention was paid to determine occurrence of even minor thromboembolic events. There was one late death during the study period. Two patients required replacement of their mitral porcine prosthesis because of paravalve regurgitation; both received a second mitral porcine prosthesis.

Autopsy cases: During the same period, five patients with a mitral porcine valve prosthesis were examined at autopsy; none were from our study group. One patient had a single mitral porcine valve; three had, in addition, an aortic valve prosthesis; and one had porcine mitral and tricuspid valves plus an aortic valve prosthesis. Each heart was examined to detect the presence of antemortem thrombi in the cardiac chambers, at the tissue-prosthesis interface or on the porcine valve cusps.

Results

Clinic patients: Thromboembolic events occurred in 5 of the 22 patients in our study group (23 percent). One patient died as a direct result of the thromboembolic event. Area of involvement, anticoagulation status and functional class at the time of the event, and the presence or absence of a history of previous thromboembolic episodes are summarized in Table I. All but Patient 5 had been taking warfarin orally at the time of the thromboembolic event. Patient 1 had a thromboembolic event 4 days after operation. Although warfarin therapy had been instituted, the prothrombin activity had not reached the desired 10 to 20 percent level. Patient 2 was in the hospital 2 of the 4 months before the thromboembolic event. During that time this patient had 49 determinations of prothrombin activity; only 14 revealed 10 to 20 percent activity. In addition, 2 months before the thromboembolic event, a repeat heart catheterization was performed and administration of anticoagulant agents was stopped for 1 week. Patient 3 had bimonthly determinations of prothrombin activity; 12 of 16 determinations were in the 10 to 20 percent range. Patient 4 had 18 determinations of prothrombin activity over the 9 month period; 13 were in the 10 to 20 percent range. Patient 5 received one of our earlier implants and was given warfarin therapy during the initial postoperative period. He received no anticoagulation therapy for 15 months before his thromboembolic event. Three of five patients with thromboembolism after porcine valve implantation had preoperative embolic events. In contrast, only 2 of the 17 pa-

TABLE II

Sites of Thromboses in Five Autopsy Cases

Case no.	Prosthetic Valves in Addition to Mitral Porcine Valve	Survival Time After Operation	Anticoagulant Status	Location of Thrombi
1	Bjork-Shiley aortic	24 hours	None	Left atrial wall
2	Smeloff-Cutter aortic	72 hours	None	None
3	Aortic porcine	8 days	None	Left atrial wall, tissue-prosthetic mitral valve interface (Fig. 1A)
4	None	30 days	Unknown	Left atrial wall, tissue-prosthetic mitral valve interface, prosthetic mitral valve cusp (Fig. 1B)
5	Bjork-Shiley aortic, tricuspid porcine	8 mo	None	Right atrial appendage

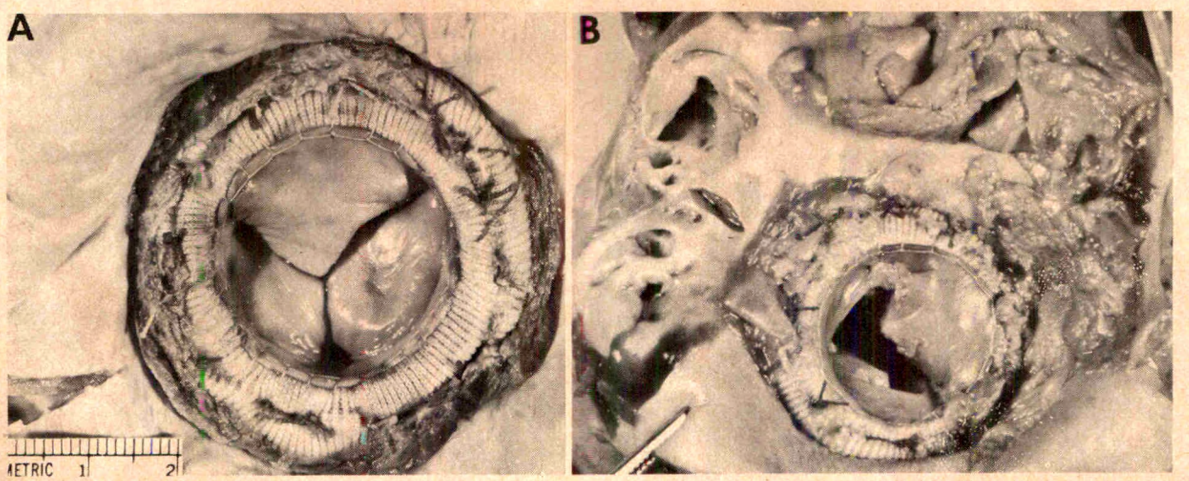

FIGURE 1. Two autopsy cases demonstrating thrombus formation. **Left,** mitral porcine heart valve from atrial side. Thrombus is present along the tissue-prosthesis interface (Case 3, Table II). **Right,** mitral porcine heart valve from atrial side. A large atrial thrombus is evident in the upper right; thrombus is also present along the sewing ring and on the valve cusps (Case 4, Table II).

tients who have been free of thromboembolism after receiving mitral porcine valves had a previous thromboembolic event. Both had a Kay-Shiley mitral valve implanted at the time of the thromboembolic event, and in both the Kay-Shiley valve demonstrated thrombi when replaced.

Autopsy cases: Five patients with a mitral porcine valve were examined at autopsy. Presence of additional valve prostheses, postoperation survival time, anticoagulation status and location of thrombus are noted in Table II. Thrombotic material was found in four of the five cases. In one case, thrombus was seen on the valve cusps (Fig. 1A); in two it was present at the tissue-valve interface (sewing ring) (Fig. 1B); and in three it was present in the left atrial chamber.

Discussion

Incidence of thromboembolism: Previous reports of thromboembolism after mitral porcine valve replacement are summarized in Table III. Four reports[5–8] show a very low incidence of thromboembolism in recipients of a single porcine mitral valve—2, 0, 2 and 5 percent, respectively. Long-term anticoagulation therapy was not routinely prescribed in any of these patient groups. The recipients of a single mitral valve described by Hannah and Reis[9] had a 12 percent incidence rate of thromboembolism. The authors imply that the incidence would have been greater if five patients who had sustained possible systemic emboli were included.

The incidence rate of thromboembolism in our clinical study group was 23 percent (5 of 22), although anticoagulation was prescribed for all patients. All of our patients had left atrial enlargement. Atrial fibrillation occurred in 18 patients, and it was the predominant rhythm in all who had emboli. Three of the five who had emboli during the study period had emboli before porcine valve implantation. The observation in our autopsy group that thrombotic material was seen on the valve cusps, at the tissue-valve interface and in the atrial chamber demonstrates that the underlying disease process, as well as the prosthetic mitral valve, continues to be a source of thromboembolic disease, even with mitral porcine valve implantation.

Possible reasons for the increased incidence of thromboembolism in our mitral porcine valve recipients are statistical variation due to sample size, close observation of a single clinic group or the presence of more advanced disease. It is also possible that anticoagulation therapy itself may have contributed to the

TABLE III

Thromboembolism in Single Mitral Porcine Valve Recipients

Reference	Period of Study	Patients (no.)	Patients with Thromboembolic Events (no.)	Incidence (%)	Anticoagulant Status
Stinson[5]	1971–1973	90	2	2	Initial 6 postoperative weeks
Cevese[6]	1968–1973	•145	0	0	No comment
McIntosh et al.[7]	1970–1974	47	1	2	None
Cohn et al.[8]	1970–1974	56	3	5	Initial 6 postoperative weeks
Hannah, Reis[9]	1970–1975	104	12*	12	Not routinely used
Present report	1974–1977	22	5	23	Routinely used*

* May be higher if "possible" systemic emboli are included.

neurologic problems.[13] Although long-term anticoagulant therapy may reduce the frequency of thromboembolic events,[1,13] canine studies[14–16] have shown that anticoagulation increased hemorrhage into experimentally produced cerebral infarctions. However, in contrast to our patients with porcine mitral prostheses, in our series of 47 similar anticoagulant treated patients with an aortic Smeloff-Cutter prosthesis followed up for a mean of 5 years, only one transient neurologic event occurred in the nonaddict population.[17]

Implications: Our study does not allow us to share the enthusiasm of previous authors who do not routinely maintain patients on anticoagulant therapy after porcine mitral valve implantation. We believe that factors influencing thrombus formation such as an enlarged left atrium, atrial fibrillation and a prosthetic device are present after mitral porcine valve implantation and are indications for long-term anticoagulation therapy.

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Tissue Valve Replacement of Prosthetic Heart Valves For Thromboembolism

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Twenty-five patients who had repeated thromboemboli from a prosthetic mitral valve were treated with reoperation using a tissue valve prosthesis. Reoperation was performed an average of 4.0 years after the original valve replacement in 14 men and 11 women, with an average age of 50 (range 35 to 65) years. A stented allograft was used in the first 7 patients and a porcine xenograft in the last 18 patients. There were one hospital death and two late deaths. With the first prosthetic valve there were 66 documented embolic episodes in 101.5 patient years (0.65 embolus/year). Only four embolic episodes in 67.4 patient years (0.059 embolus/year) occurred after tissue valve replacement ($P < 0.001$). These results indicate that in patients with recurrent or severe embolization after prosthetic heart valve replacement, rereplacement with a tissue prosthesis can be safely performed and significantly reduces the likelihood that additional embolic episodes will occur.

Systemic embolization is a serious and dreaded complication of prosthetic heart valve replacement. Although different mechanical prostheses may vary in their thrombogenic potential, all are susceptible to thrombus formation and require indefinite postoperative anticoagulation in order to minimize the risk of thromboembolism.[1] Furthermore, some patients may be relatively more prone to systemic thromboembolism after mechanical heart valve replacement because of structural cardiac deformity, cardiac arrhythmia, hypercoagulable state or difficulty in maintenance of an effective anticoagulant regimen. Thus, thromboembolism constitutes a major cause of prosthesis-related morbidity and mortality in most large reported series of heart valve replacement. In general, this problem is more severe after mitral than after aortic valve substitution.

We have treated 25 patients with an isolated mitral valve prosthesis associated with repetitive thromboembolic episodes by reoperation and replacement of the prosthesis with a tissue valve. In this report we review this clinical experience and document the usefulness of this strategy in the treatment of multiple embolic episodes after prosthetic valve replacement.

Patients and Methods

Patients: Between June 1967 and May 1975, a total of 25 patients underwent reoperation because of repeated thromboembolic episodes after prosthetic mitral valve replacement. The patients ranged in age from 35 to 65 years (mean 50 years); 14 were men. Twenty-one patients had received a Starr-Edwards model 6120 prosthesis, three a Starr-Edwards 6320 valve and one patient a Harken disc valve. All had been treated with chronic anticoagulant therapy with warfarin sodium after prosthetic valve replacement, but details of the adequacy of anticoagulation control were not available. Four patients had sustained a systemic embolic event before prosthetic valve implantation.

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TABLE I

Tissue Valve Replacement for Thromboembolism in 25 Patients

	Prosthetic Valve	Tissue Valve
Embolic events (no.)		
CNS	62	3
Peripheral	3	1
Myocardial	1	0
Total	66	4
Emboli/patient (no.)	2.6	0.16*
Average interval (yr)	4.0	2.9
Patient-years	101.5	67.4
Emboli/year	0.65	0.059*

* Probability (P) <0.001.
CNS = central nervous system.

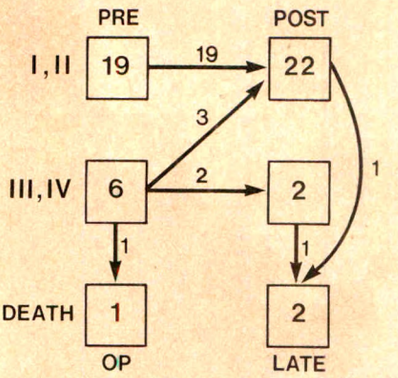

FIGURE 1. Functional class (New York Heart Association) and operative and late mortality of 25 patients undergoing tissue valve replacement of a prosthetic heart valve because of thromboembolism. OP = operative death; POST = postoperative; PRE = preoperative.

Thromboembolic events: Rheumatic mitral valvulitis constituted the underlying etiologic disease in 21 of the 25 patients (84 percent). Fifteen patients had stable normal sinus rhythm and 10 had chronic atrial fibrillation. A total of 66 documented systemic thromboembolic events had occurred during a total of 101.5 patient-years before reoperation (linearized embolism rate 65 percent per patient-year). The majority of these consisted of cerebral emboli (62 episodes); there were also three instances of peripheral emboli in the limbs and one instance of myocardial embolus causing infarction (Table I). The number of embolic episodes per patient ranged from 1 to 9 (average 2.6 embolic episodes per patient). The distribution of emboli with time varied widely from 1 month to 7 1/2 years postoperatively.

On the basis of symptoms at the time of reoperation, most patients (76 percent) were in functional class I or II (New York Heart Association criteria[2]), but four were in functional class III and two in functional class IV. The more severely limited patients had associated aortic valve disease (one patient), ventricular dysfunction (three patients) or prosthetic valve malfunction due to thrombotic restriction of poppet motion (two patients). Therefore, in the majority of patients, the decision for reoperation was predicted entirely upon a history of repetitive thromboembolism.

Reoperation: This was performed an average of 4.0 years after original prosthetic valve implantation. Standard techniques for repeat median sternotomy and for cardiopulmonary bypass were used.[3] The aorta was cross-clamped during excision of the prosthetic valve and placement of sutures. Aortic cross-clamp time ranged from 27 to 123 minutes (average 57); during periods of cross-clamping, myocardial protection was provided by topical hypothermia afforded by continuous lavage of the pericardial well with 0.9 percent saline solution at 3 to 4° C. The left ventricle was vented with a tailored T tube placed across the valve and brought out through the left atriotomy until after ventricular defibrillation. In one patient the aortic valve was also replaced and in another a left carotid thromboendarterectomy was performed concomitantly.

The first seven patients received a stented fresh aortic valve allograft[4,5] and the remaining 18 patients a Hancock porcine aortic valve xenograft. Current follow-up evaluation was obtained by direct contact with the patient or physician or both. The average follow-up interval for surviving patients was 2.9 years (range 2 months to 8.2 years). The total duration of follow-up for all patients after reoperation was 67.4 patient-years.

Results

Early mortality and complications: One patient died of myocardial failure early after reoperation (operative mortality rate 4 percent). This patient had advanced functional disability (class IV) and had required, in addition to mitral valve replacement, aortic valve replacement because of aortic regurgitation. Perioperative complications included one immediate reoperation because of excessive postoperative hemorrhage, one wound infection and one episode of femoral arterial thromboembolism requiring embolectomy.

Late mortality and complications: Two patients died during the late postoperative period. One died 4 1/2 months after reoperation as a result of progressive left ventricular failure that was not alleviated by xenograft valve replacement of a Starr-Edwards prosthesis obstructed by massive thrombus deposition. The other late death occurred 3 years after reoperation and was due to calcific degeneration of an allograft substitute.[5] Additional late complications included two repeat reoperations for failure of homograft valves 3 and 7 years postoperatively, respectively. Patients receiving porcine xenograft valves have been notably free of valve-related complications.

Postoperative functional classification of surviving patients shows continued well-being or improvement in the majority. Sixteen patients are in functional class I, five in class II and one in class III (Fig. 1). Fifteen patients continue to have normal sinus rhythm and seven have atrial fibrillation.

Thromboembolic complications: Anticoagulation was continued in 14 patients and discontinued in 8. Only two patients sustained thromboembolic complications (three episodes in one patient, one in the other) after tissue valve implantation. One was the patient described earlier who had a femoral arterial embolus 2 weeks postoperatively before discharge from the hospital. The second patient had three mild cerebrovascular events diagnosed as embolism during 36 months of follow-up, but the nature of these events is not well established

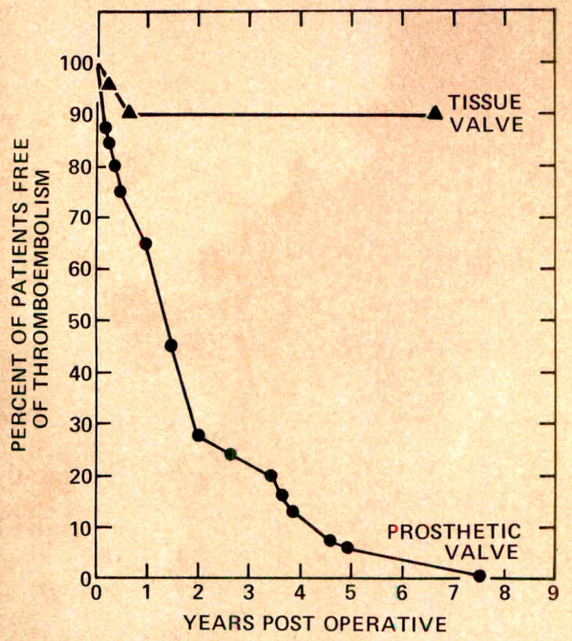

FIGURE 2. The percent of 25 patients free of a thromboembolic event after mitral valve replacement. **Closed circles** indicate prosthetic valve and **closed triangles** indicate tissue valve.

because he has known cerebrovascular disease and underwent associated carotid thromboendarterectomy at the time of reoperation. He presented with new transient neurologic deficits related to the cerebral hemisphere contralateral to the site of endarterectomy 9 months postoperatively and subsequently had cerebrovascular deficits on the side of the endarterectomy 15 and 26 months postoperatively. He also retained severe enlargement of the left atrium and continued to have chronic atrial fibrillation.

The total number of diagnosed embolic episodes during 67.4 patient-years of follow-up after tissue valve implantation yields a linearized embolization rate of 5.9 percent per patient-year. This rate is markedly lower ($P < 0.001$) than the preoperative rate of 65 percent per patient-year in these same patients (Table I). Actuarial analysis of the incidence of thromboemboli, expressed as the probability that a patient will be free from this complication, is illustrated in Figure 2. The greatly diminished risk of further thromboembolism after tissue valve replacement of a mechanical prosthesis is highly significant ($P < 0.001$).

Discussion

Mitral valve disease is recognized to be associated with an increased risk of systemic embolization. This is especially true in the case of mitral stenosis with atrial fibrillation and enlargement of the left atrium. The occurrence of four thromboemboli before original valve replacement in our series of 25 patients illustrates this predisposition.

The relatively increased risk of thromboembolic complications after replacement of the mitral valve with a mechanical prosthesis, as compared with aortic prosthetic valve replacement, has been well documented. In addition to the risk imposed by mitral valve prostheses, the same factors that apply before operation appear to continue to influence the likelihood of thromboembolism after valve replacement. This contention is supported by the observation that during the period covered by this report (1967 to 1975) we encountered no patients with isolated aortic prosthetic valve replacement who required reoperation on the basis of recurrent thromboembolic episodes.

Allograft grafts: During the initial years (1967 to 1970) of our experience with reoperation for thromboemboli, we used fresh aortic allograft valves mounted on Dacron®-covered stents.[4,5] The early postoperative performance of these bioprostheses was satisfactory in regard to operative mortality rate, hemodynamic function and low risk of thromboembolism.[5] However, long-term follow-up demonstrated a prohibitively high failure rate requiring repeat operative intervention (linearized reoperation rate 3.2 percent per patient year).[6] Among the eight patients who received allografts in the present series, one died early postoperatively, one late postoperatively because of valve deterioration and two required an additional reoperation, performed successfully.

Porcine xenograft bioprosthesis and indications for anticoagulation therapy: In contrast, the results with porcine xenograft bioprostheses, used in 17 patients in the present study, have been excellent in terms of valve durability and low risk of thromboembolism. Several centers have now reported clinical experience with this tissue prosthesis through maximal follow-up intervals in excess of 5 years.[7–10] Within the constraints of this time period, the durability of xenograft valves appears comparable to that of mechanical prostheses. The majority of thromboemboli (74 percent) in patients with porcine xenografts occurred during the first 3 postoperative months.[11] Theoretically, this marked skewing of the time distribution of thromboemboli after xenograft valve replacement may be attributed primarily to the exposed Dacron elements of the valve. Gradual endothelialization of this thrombogenic surface presumably occurs during the first several weeks after operation and is associated with a subsequent decrease in the risk of thrombus formation and embolism; the incidence of thromboemboli after the first 3 postoperative months is significantly less than that observed early postoperatively.[11] For this reason we now recommend for patients undergoing porcine xenograft mitral valve replacement anticoagulation during the initial 3 postoperative months, followed by tapering and discontinuation unless intercurrent thromboembolism has occurred or the patient has intermittent atrial fibrillation. Fourteen of the 23 surviving patients of this series have been maintained on long-term oral anticoagulant therapy.

Indications for reoperation: The results of this select experience with tissue valve replacement of mechanical prostheses for recurrent thromboembolism confirm the clinical usefulness of this procedure. The two primary indications for reoperation are (1) two or more episodes of thromboembolism despite satisfactory maintenance anticoagulation, and (2) evidence of prosthetic valve dysfunction due to obstructing thrombus. Our results indicate that reoperation can be safely accomplished in patients meeting these criteria and that the likelihood of further thromboembolic complications is significantly reduced.

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Central Neurochemical Factors Related to Serotonin Metabolism and Cardiac Ventricular Vulnerability For Repetitive Electrical Activity

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Sympathetic neural activity modifies cardiac excitability and lowers the threshold of the vulnerable period for ventricular fibrillation. Sympathetic neural traffic to the heart can be diminished by administering serotonin precursors that localize in the central nervous system. In this study anesthetized dogs were injected with either of the serotonin precursors L-tryptophan or 5-hydroxy-L-tryptophan in conjunction with the monoamine oxidase inhibitor phenelzine and the selective peripheral L-amino acid decarboxylase inhibitor carbidopa. Ventricular vulnerability was evaluated by measuring the repetitive extrasystole threshold. A sustained increase of 50 percent in this threshold resulted only with use of biochemical measures that presumably increase serotonin levels in the central nervous system. Thus neuropharmacologic measures affecting central sympathetic activity alter cardiac vulnerability and may protect against ventricular fibrillation.

It has long been recognized that sympathetic neural activity predisposes to cardiac arrhythmias and increases cardiac vulnerability to ventricular fibrillation.[1–6] Enhanced sympathetic activity, whether elicited by electrical stimulation of hypothalamic centers[7] or of stellate ganglia,[8,9] augments cardiac susceptibility to diverse arrhythmias. Similar effects can be induced with sympathomimetic drugs.[10–15] Conversely, the heart can be protected against arrhythmias by reduction of sympathetic neural traffic achieved either surgically[8,16–22] or pharmacologically.[10,15,23–28] Sympathetic tone can also be lessened reflexly by baroreceptor activation. Verrier et al.[29] found that the ventricular fibrillation threshold is raised by increasing systemic arterial pressure using either pressor drugs or mechanical means. This effect of acute hypertension was shown to be mediated by withdrawal of sympathetic activity because it occurred despite vagotomy. Blatt et al.[30] similarly demonstrated that increases in blood pressure prevent the lowering of the vulnerable period threshold that occurs during coronary occlusion. One might therefore anticipate that a reduction of sympathetic neural outflow from the brain would likewise affect cardiac vulnerability. However, no studies of this phenomenon have been reported.

A method for inhibiting sympathetic neural traffic was recently described.[31–33] It requires the intravenous administration of a biochemical precursor of serotonin, either L-tryptophan or 5-hydroxy-L-tryptophan (Fig. 1). Pretreatment with the decarboxylase inhibitor carbidopa, which circulates peripherally without crossing the blood-brain barrier, tends to restrict formation of serotonin to the central nervous system. Because the serotonin that forms would rapidly oxidize, the systemic monoamine oxidase inhibitor phenelzine is given to protect serotonin from degradation. The result is formation and accumulation of serotonin within the central nervous system but not in the periphery.

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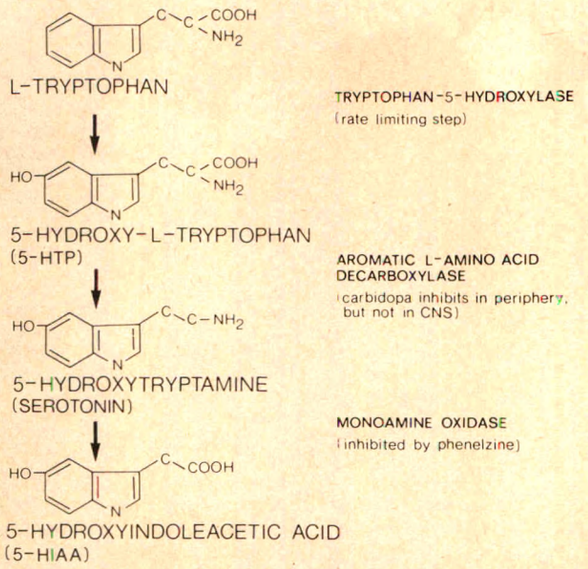

FIGURE 1. The major metabolic pathway of serotonin showing the actions of carbidopa and phenelzine. CNS = central nervous system.

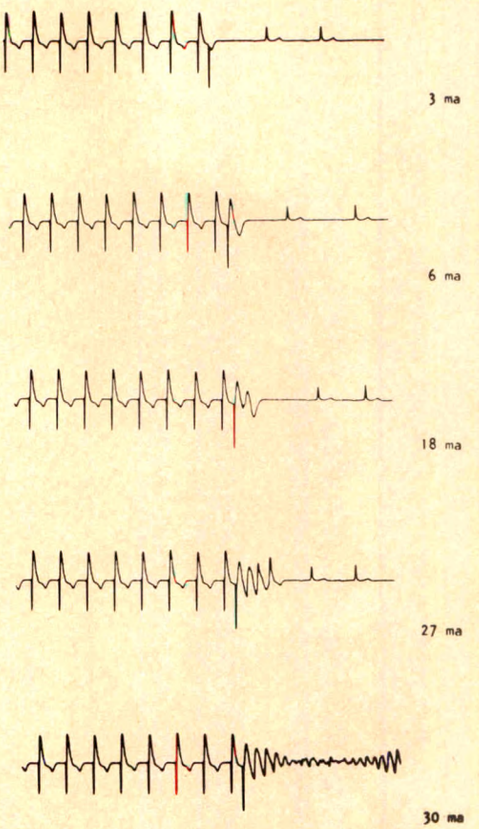

FIGURE 2. Responses of a ventricular-paced canine heart to single premature impulses of various current intensities. The threshold for repetitive extrasystoles is 18 milliamperes (ma) in this instance, and the ventricular fibrillation threshold is 30 ma.

The aim of this study was to determine whether neuropharmacologic measures that presumably increase serotonin levels in the central nervous system raise the threshold of the vulnerable period for repetitive ventricular activity. Cardiac vulnerability was evaluated with the repetitive extrasystole method previously developed in this laboratory[15,34] (Fig. 2).

Materials and Methods

General Protocol

Eighteen healthy mongrel dogs of either sex, at least 1 year old, weighing 6.5 to 19 kg, were studied. Food, but not water, was withheld for 18 hours before the experiments. The animals were anesthetized intravenously with 50 mg/kg body weight of alpha-chloralose (Sigma Chemical) 1 percent weight in volume in isotonic saline solution. The chloralose was dissolved at 80 °C. The resulting solution was cooled to 37° before injection. This and all other agents used were freshly prepared before use. Additional chloralose, 50 mg/kg, was given when required to maintain a constant plane of anesthesia during the experiment. Electrical testing of the heart was delayed until at least 30 minutes after anesthetic administration. The animals were ventilated with room air by means of a cuffed endotracheal tube using a Harvard respiratory pump set at a rate of 14/min. The tidal volume was adjusted to maintain arterial blood pH at 7.35 to 7.45. Rectal temperature was continuously monitored. Cooling or warming was utilized to preserve a level between 37 and 39 °C. A polyethylene catheter was inserted into the right femoral vein for infusing anesthetic and other drugs specified later. The right femoral artery was cannulated for sampling arterial blood and for monitoring pressure, which was accomplished with a Statham P23 dB transducer, American Optical preamplifier and oscilloscope. Mean pressures were obtained by electrically integrating the phasic transducer output and converting the analog signal to a binary-coded decimal number for readout by a Tektronix 31 programmable calculator. The system was calibrated against a standard mercury manometer. Pressure and heart rate determinations were made immediately after repetitive extrasystole threshold measurements.

Cardiac Testing

Electrical testing of the heart was accomplished using an intracavitary lead system, as previously reported.[15,34] The unit consists of two catheters bound together side by side with silk suture. One catheter was used to record the electrocardiogram (Elecath, 5 by 1 mm electrodes, 8 mm apart) and the other to deliver both pacing and testing impulses to the heart (Medtronic, 5 by 3 mm electrodes, 16 mm apart). The pacing catheter protrudes 30 mm beyond the tip of the recording catheter. Guided by fluoroscopic visualization, the combined catheters were passed through a jugular vein and positioned against the interventricular septum to the right of the ventricular apex. The distal electrode of the recording catheter and a left forelimb needle electrode were used to provide a continuous oscilloscopic display (American Optical) of the intraventricular electrogram.

A specially designed numerically controlled device was programmed with one of the Tektronix 31 calculator and Tektronix 152 interface to deliver both pacing and testing impulses. The device consists of an interval delay generator and an electrically isolated, constant current pulse generator. The system is accurate to 0.1 msec and 0.1 milliamperes (ma). All impulses were of 2 msec duration and of rectangular wave form. Pacing was performed at intervals of 280 msec. This rate (214 beats/min) permitted override of the highest spontaneous

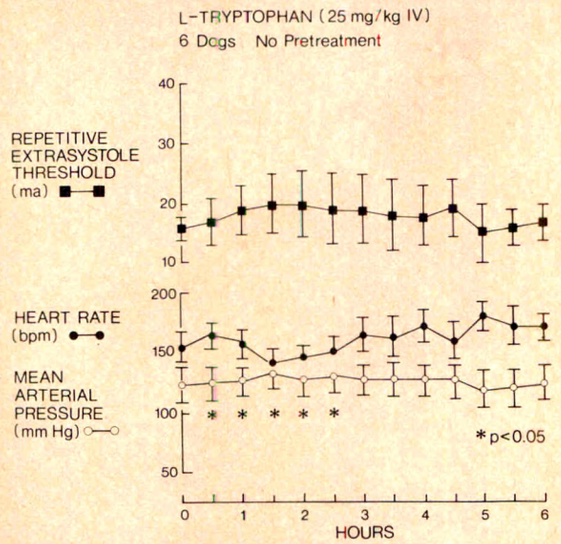

FIGURE 3. Changes in repetitive extrasystole threshold, heart rate (beats/min [bpm]) and blood pressure in six dogs after intravenous (IV) injection of L-tryptophan, 25 mg/kg.

heart rates encountered. The pacemaker current was adjusted to twice the mid diastolic threshold or to a minimum of 2 ma. The distal pole of the pacemaker was made cathodal.

Determination of the repetitive extrasystole threshold was accomplished by means of a testing cycle lasting 4 seconds. During the first 3 seconds the heart rate was maintained constant by pacing. A test impulse was then delivered. After a 1 second pause, the next test cycle commenced. During the 1 second pause, the electrocardiographic response to the test impulse was digitally processed by the calculator for detection of repetitive extrasystoles. Responses were instantly replayed from the calculator memory to a Tektronix 5103 N storage oscilloscope. Human monitoring confirmed every machine-made decision. Test impulses were delivered in successive cycles beginning with the mid point of the T wave and progressing earlier by 2 msec intervals until the refractory period was reached. A 2 ma stimulus was used for this exploration. If no repetitive extrasystole resulted, the interval was rescanned with a stimulus increased by 1 ma steps. Once 20 ma was reached, 2 ma increments were used. The repetitive extrasystole threshold was taken to be the minimal current intensity at which a single stimulus evoked a dual response in two of three trials.

In the uncommon instance in which ventricular fibrillation developed, the heart was defibrillated within 15 seconds by a direct-current capacitor discharge (200 joules from a Lown cardioverter) delivered through a pair of copper plates (100 cm^2) that were previously secured to either side of the thorax.

Drugs

The following solutions were freshly prepared before each administration: L-tryptophan (Sigma Chemical), an essential dietary amino acid and serotonin precursor, was dissolved in normal saline solution, 5 mg/ml; 5-hydroxy-L-tryptophan (Sigma Chemical), the product of the rate-limiting hydroxylation step in the synthesis of serotonin from L-tryptophan and the immediate biochemical precursor of serotonin, was dissolved in normal saline solution, 5 mg/ml. Phenelzine (Nardil®, Warner-Lambert), a monoamine oxidase inhibitor, was dissolved in distilled water, 50 mg/ml. Carbidopa (MK-486, Merck), a selective peripheral aromatic L-amino acid decarboxylase inhibitor, was dissolved, 5 mg/ml in normal saline solution acidified to pH 1.5 (97 ml normal saline/3 ml 2N hydrochloric acid).

TABLE I

Control Studies in 12 Dogs (mean ± standard error of the mean)

	Chloralose	Chloralose + Phenelzine	Chloralose + Phenelzine + Carbidopa
Heart rate (beats/min)	159 ± 9	143 ± 9	139 ± 10
Mean arterial pressure (mm Hg)	126 ± 8	113 ± 7	115 ± 7
Repetitive extrasystole threshold (ma)	18 ± 2	17 ± 1	21.5 ± 2*

* This threshold value is statistically significantly higher than that after chloralose and phenelzine ($P = 0.01$) but not significantly different from that after chloralose alone.

Six dogs, constituting a control group, were treated with L-tryptophan alone. After 25 mg/kg was injected intravenously, the repetitive extrasystole threshold, spontaneous (unpaced) heart rate and arterial pressure were determined every 30 minutes for 6 hours.

In 12 animals phenelzine, 20 mg/kg, was injected intraperitoneally to inhibit monoamine oxidase. These dogs were anesthetized 18 hours later and had repetitive extrasystole threshold measurements. Thereafter, these animals received carbidopa, 25 mg/kg intravenously, which circulates peripherally but does not penetrate the blood-brain barrier. Thirty minutes after carbidopa was administered, the repetitive extrasystole threshold was again tested.

In 6 of the 12 animals, L-tryptophan, 25 mg/kg, was injected intravenously, and repetitive extrasystole testing was carried out every 30 minutes for 6 hours. The remaining 6 dogs received 5-hydroxy-L-tryptophan, 25 mg/kg intravenously, and were tested in similar fashion and the repetitive extrasystole threshold was monitored for 4 hours.

The results were analyzed using the appropriate Student t test for independent or paired data. The criterion of significance was $P < 0.05$.

Results

Control groups: *In 12 dogs anesthetized with chloralose,* the repetitive extrasystole threshold was 18 ± 1.5 ma (mean ± standard error of the mean), the spontaneous (unpaced) heart rate 159 ± 9 beats/min and the mean arterial pressure 126 ± 8 mm Hg. After administration of L-tryptophan to six animals, there was no significant change in these values (Fig. 3). During the 6 hours of observation, the repetitive extrasystole threshold value ranged from a low of 16 ± 5 to a high of 20 ± 6 ma. Heart rate ranged from 143 ± 9 to 179 ± 12 beats/min; arterial pressure remained stable.

In the 12 animals receiving phenelzine, the repetitive extrasystole threshold 18 hours later was not significantly different from that observed in dogs anesthetized with chloralose. Thirty minutes after the intravenous injection of carbidopa, heart rate and blood pressure were not significantly altered. The repetitive extrasys-

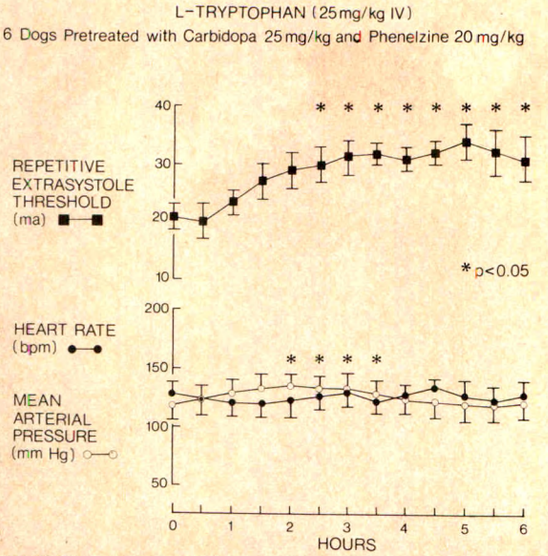

FIGURE 4. Changes in repetitive extrasystole threshold, heart rate and blood pressure after L-tryptophan, 25 mg/kg, was injected intravenously (IV) into six dogs pretreated with carbidopa, 25 mg/kg, and phenelzine, 20 mg/kg. p = probability.

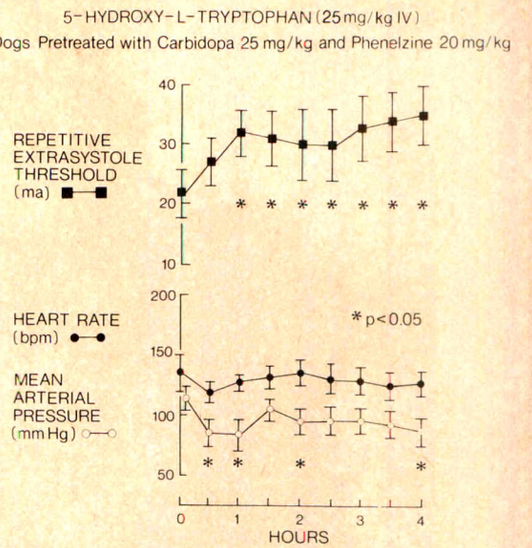

FIGURE 5. Changes in repetitive extrasystole threshold, heart rate and blood pressure after 5-hydroxy-L-tryptophan, 25 mg/kg, was injected intravenously (IV) into six dogs pretreated with carbidopa 25 mg/kg and phenelzine 20 mg/kg.

tole threshold value of 21.5 ± 2 was higher than the value noted after phenelzine (P = 0.01) but was not different from that in the chloralose-anesthetized animals (Table I).

L-tryptophan in phenelzine- and carbidopa-pretreated animals: In these six dogs pretreated with phenelzine and carbidopa, the repetitive extrasystole threshold was 20 ± 2 ma. After injection of L-tryptophan there was a progressive rise in threshold to a value of 30 ± 3 ma (P = 0.02) at 150 minutes. It persisted at about this level for the duration of the experiment although an increase to 34 ± 3 ma was recorded at 5 hours. Heart rate ranged from 120 ± 12 to 135 ± 6 beats/min. The mean arterial pressure of 117 ± 13 increased to a peak of 135 ± 11 mm Hg (P = 0.017) 120 minutes after the administration of L-tryptophan (Fig. 4).

5-hydroxy-L-tryptophan in phenelzine- and carbidopa-pretreated animals: Six animals received this natural product of the rate-limiting hydroxylation step that precedes decarboxylation to serotonin (Fig. 1). One would therefore anticipate an accelerated onset of serotonin accumulation when the rate-limiting step in the formation of serotonin is bypassed. Before the injection of 5-hydroxy-L-tryptophan, the repetitive extrasystolic threshold was 22 ± 4 ma. Within 1 hour after injection, the threshold reached 32 ± 5 ma (P = 0.02) (Fig. 5). The repetitive extrasystole threshold remained significantly elevated, ranging between 30 ± 6 and 35 ± 5 ma until the experiment was terminated 4 hours after injection. The development of severe hypotension in four dogs precluded continuation of this study beyond 4 hours. The initial mean blood pressure was 114 ± 8 and significantly decreased to 86 ± 11 mm Hg (P = 0.01) within 30 minutes after injection of 5-hydroxy-L-tryptophan. Mean blood pressure ranged from 85 ± 11 to 105 ± 15 mm Hg over the 4 hours of these experiments. No significant deviation from the control heart rate of 135 ± 15 beats/min occurred (range 118 ± 8 to 136 ± 9).

Discussion

Advantages of repetitive extrasystole threshold method as an index of ventricular vulnerability to arrhythmias: These experiments show that compared with control conditions 50 percent more electrical current is required to provoke repetitive extrasystoles in the canine ventricle after the administration of drug combinations that purportedly increase serotonin concentration in the central nervous system. The repetitive extrasystole threshold model, used extensively in our laboratory,[15,34] was selected as an index of ventricular vulnerability to arrhythmias. We have found that the repetitive extrasystole threshold current correlates quantitatively to 66 percent of the ventricular fibrillation threshold current, and the timing of the vulnerable period in the cardiac cycle of the two methods coincides under diverse neural interventions (Fig. 2).[34] The repetitive extrasystole method has three advantages over the widely used method of measuring ventricular fibrillation threshold. (1) The provocation of ventricular fibrillation and defibrillation may engender autonomic disturbances that would obscure the variables being assessed. (2) Provocation of ventricular fibrillation is unsuitable for studies in conscious animals, which are essential to a more definitive appraisal of psychoneural influences on arrhythmia. (3) Repetitive extrasystoles can be repeatedly elicited to distinguish consistent from sporadic responses with much greater facility than when ventricular fibrillation is used as the end point.

Effect of tryptophan in animals pretreated with carbidopa and phenelzine: Significant sustained increases in repetitive extrasystole threshold attended the administration of tryptophan to animals pretreated with both carbidopa and phenelzine (Fig. 4). No such increase occurred when animals were given tryptophan alone (Fig. 3) or carbidopa and phenelzine alone (Table I). This finding indicates that the three agents have no direct effect on cardiac vulnerability. Only when the drugs interact is there an effect. The nature of this interaction is suggested by an analysis of tryptophan metabolism (Fig. 1). Tryptophan is an essential dietary amino acid and the physiologic biochemical precursor of serotonin. When tryptophan alone is administered, it is hydroxylated and then decarboxylated to form serotonin at sites throughout the body. Monoamine oxidase then catalyzes a rapid degradation of the serotonin. This sequence is altered in two important ways by phenelzine and carbidopa. Phenelzine inhibits monoamine oxidase so that serotonin tends to accumulate wherever it is formed. Carbidopa is an L-aromatic amino acid decarboxylase inhibitor that circulates in the periphery but does not cross the blood-brain barrier. In the presence of carbidopa the decarboxylation of precursor to serotonin is selectively diminished peripherally and therefore largely restricted to within the central nervous system. One would therefore expect that administration of tryptophan or 5-hydroxytryptophan to animals pretreated with phenelzine and carbidopa would result in the formation and accumulation of serotonin within the central nervous system but not in the periphery. The concentration of serotonin in the brain has indeed been shown to depend on plasma levels of tryptophan.[35] Serotonin accumulation in the brain has been demonstrated in rats after administration of tryptophan and a monoamine oxidase inhibitor.[36]

Hemodynamic and neuroreflex effects: 5-Hydroxytryptophan, administered to dogs by Antonaccio and Robson,[31,32] had no effect on blood pressure or heart rate. 5-Hydroxytryptophan is not directly subject to oxidative degradation. However, because serotonin, the decarboxylation product of 5-hydroxytryptophan, is subject to oxidative deamination, Antonaccio and Robson gave a monoamine oxidase inhibitor to a group of dogs before 5-hydroxytryptophan administration. Blood pressure decreased, as in our experiments. A lower rate of rise of left ventricular pressure (dP/dt) and progressive severe depression of reflex pressor and cardiac accelerator responses to bilateral carotid arterial occlusion were noted. The dependency of these results on monoamine oxidase inhibition suggests mediation of the effects by serotonin. Antonaccio and Robson also conducted trials in which the selective peripheral decarboxylase inhibitor carbidopa was replaced with RO 4-4602, which inhibits both extracerebral and cerebral decarboxylase. Serotonin formation from 5-hydroxytryptophan was thus blocked in the brain as well as in the periphery. Effects of 5-hydroxytryptophan on blood pressure and bilateral carotid occlusion reflexes were then markedly attenuated. Inhibition of these 5-hydroxytryptophan effects was also accomplished by administration of the serotonergic receptor antagonist methysergide.[32]

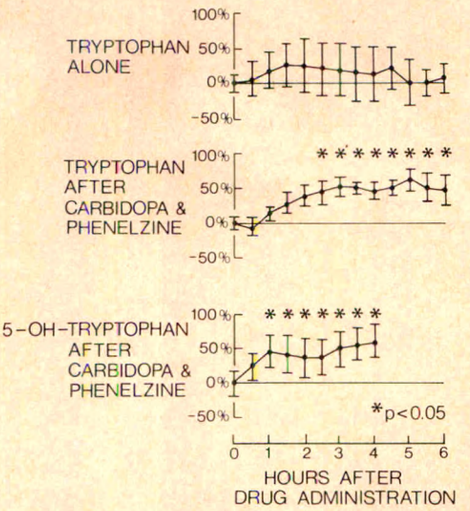

FIGURE 6. Repetitive extrasystole threshold changes observed after the administration of three different drug regimens. Six dogs were tested in each group. **Vertical lines with bars** represent ± standard error of the mean.

Serotonin synthesis and effect on repetitive extrasystole threshold: The time sequence of changes in repetitive extrasystole threshold in our experiments also supports the hypothesis that the changes were mediated by serotonin synthesis. L-tryptophan must undergo hydroxylation in the body before decarboxylation to serotonin can occur (Fig. 1). The rate-limiting hydroxylation step can be bypassed by the administration of its natural product, 5-hydroxytryptophan. One would anticipate an accelerated onset of serotonin accumulation when the rate-limiting step is circumvented in this manner. We administered L-tryptophan to one group of animals and the hydroxylated product to another. After either compound was given to animals pretreated with phenelzine and carbidopa, significant and sustained increases in repetitive extrasystole threshold of about 50 percent were observed; that is, the electrical current intensity required to provoke repetitive extrasystoles was 50 percent greater than during the control state. The threshold increased in 1 hour after administration of the hydroxy compound compared with 2 1/2 hours after tryptophan (Fig. 6). This provides further evidence that an increase in serotonin in the central nervous system mediated the threshold response. The development of hypotension in the group given 5-hydroxytryptophan, in contrast to essentially normal pressure in the group given tryptophan, suggests that the rate and extent of endogenous hydroxylation prevents this more profound central serotonin effect when natural tryptophan is administered.

Mechanism of serotonin effect on cardiac vulnerability: How then does alteration of the serotonin level in the central nervous system affect cardiac vulnerability? In the aforementioned investigations of

Antonaccio and Robson[31,32] the putative effects of serotonin on the central nervous system consisted of hypotension mediated mainly by decreased peripheral resistance, decreased left ventricular dP/dt and depressed carotid occlusion reflexes. These alterations are consistent with decreased sympathetic neural traffic outflow from the central nervous system. It is therefore relevant to note the neural traffic recording study of Baum and Shropshire.[33] They examined electrical activity in cardiac, renal and splanchnic sympathetic nerves of anesthetized cats. After peripheral decarboxylase inhibition with carbidopa, the systemic administration of 5-hydroxytryptophan resulted in dose-related reduction of as much as 87 percent in efferent traffic. Similar results attended administration of either 5-hydroxytryptophan or 5-hydroxytryptamine (serotonin) into the feline brain ventricular system. If the increase in serotonin in the central nervous system resulted in reduced outflow of sympathetic neural traffic to the heart, then the increase in repetitive extrasystole threshold is consistent with our knowledge of sympathetic neural influence on the heart. Surgical sympathectomy protects the heart from arrhythmia.[16–22] Pharmacologic blockade of sympathetic tone is likewise protective and elevates the repetitive extrasystole threshold.[10,15,23–28]

Implications: Statistically significant increases in current intensity were required to provoke repetitive extrasystoles after procedures designed to increase serotonin in the central nervous system. The procedures presumably inhibit efferent sympathetic traffic to the heart. Although neither brain serotonin concentration nor sympathetic neural traffic was directly measured in our study, we believe that the serotonin-sympathetic relation is the most logical basis for the observed changes in repetitive extrasystole threshold.

Lown and Verrier[37] reviewed evidence that sympathetic neural traffic to the heart can transiently lower the vulnerable period threshold of an electrically unstable myocardium and thereby facilitate the onset of ventricular fibrillation. They concluded, "It may be that pharmacologic treatments for prevention of sudden death should be focused on restraining the neurophysiologic triggers rather than protecting the cardiac target." The present investigation indicates the feasibility of reducing ventricular vulnerability by neuropharmacologic measures.

Acknowledgments

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Experimental Myocardial Infarction. XVI. The Detection of Inotropic Contractile Reserve With Postextrasystolic Potentiation in Acutely Ischemic Canine Myocardium

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Postextrasystolic potentiation after a single closely coupled extrasystole may identify residual ventricular contractile performance in acutely ischemic myocardium without producing sustained secondary ischemic depression of myocardial function. Postextrasystolic potentiation was systematically used in eight open chest dogs to assess the progression of regional contraction abnormalities during a 10 minute occlusion of the left anterior descending coronary artery. Segment function was determined from pressure-length loop areas inscribed during right ventricular pacing at 128 ± 3 (mean ± standard error of the mean) beats/min, and after single closely coupled (179 ± 3 msec) extrasystoles. Despite a 50 percent decrease in border zone segment function, postextrasystolic potentiation consistently augmented mechanical performance to control levels throughout the ischemic period. Central ischemic zone segment function deteriorated more profoundly, with the development of holosystolic aneurysmal bulging within 30 seconds after occlusion. Nonetheless, postextrasystolic potentiation produced marked inotropic augmentation, but not to control levels, for up to 10 minutes of ischemia. These results suggest that latent viability and contractile reserve may exist during brief periods of coronary occlusion.

Pump failure in acute myocardial ischemia and infarction results from loss of contracting myocardium and focal dyskinesia.[1–3] By restoring flow to areas that are ischemic but still viable, coronary revascularization may improve segment and overall ventricular function.[4–6] Effective use of coronary revascularization is therefore predicated on the preoperative recognition of residual ventricular contractile function, which may be masked in the presence of ischemia. Both pharmacologic inotropic stimulation[2,7,8] and postextrasystolic potentiation[2,8–10] have been used to detect latent contractile reserve in experimental and clinical studies of cardiac ischemia. The use of prolonged inotropic interventions is limited because responses may be attenuated[11] or result in sustained secondary ischemic depression of myocardial function due to accelerated oxygen needs, especially when coronary blood flow is limited.[12] However, a single paired extrasystole may be used to detect viable but poorly contracting myocardium without causing sustained myocardial depression or increasing ischemic injury.[8,9]

Heretofore there has been no systematic evaluation of the potentiation of contractile state that follows a single closely coupled extrasystole in assessing the progression of regional contraction abnormalities of acutely ischemic cardiac muscle. Accordingly, this study was performed (1) to quantify precisely changes in regional mechanical performance utilizing pressure-length loops as an index of segment work,[13,14] and (2) to compare these intrinsic mechanical responses with the potentiated con-

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tractile responses after closely coupled extrasystoles during acute coronary occlusion while heart rate and coupling interval were held constant.

Methods

Protocol: Eight adult mongrel dogs weighing 23.2 ± 1.3 kg (mean ± standard error of the mean) were anesthetized with intravenously administered chloralose, 30 mg/kg body weight, and urethane, 450 mg/kg. Small supplemental doses of these agents were administered as required. After endotracheal intubation, positive pressure ventilation with 40 percent oxygen in air was maintained with a Bennett model PR-2 respirator. A thoracotomy was performed through the fifth left intercostal space and the heart suspended in a pericardial cradle. The left anterior descending coronary artery was isolated distal to the first diagonal branch, and a snare occluder placed around it for inducing ischemia (Fig. 1). A bipolar pacing electrode was attached to the right ventricle and connected to a Grass model S44B pulse stimulator.

To assess regional function, we used methods previously described by this laboratory.[2,15] After calibration, three mercury-in-Silastic® length gauges with an inner and outer diameter of 0.32 and 0.64 cm, respectively (Parks Electronics, Beaverton, Oregon) were inserted into small (8 mm diameter) Teflon® holders sutured directly to the epicardium (Fig. 1). One was placed in the central zone of distribution of the left anterior descending coronary artery, one along the border zone* and one in a zone of normal myocardium remote from the area of infarction. Previous studies[2] have demonstrated stable linearity and gain in these gauges.

Hemodynamic measurements of aortic and left ventricular pressures were obtained using, respectively, an end-hole catheter passed retrograde from the femoral artery and a 10 cm long no. 240 polyethylene catheter (with a natural frequency of 50 hertz) inserted directly through the apex of the ventricle. The zero level for pressure measurements was set at midchest level. The catheters were attached to Statham P23Db pressure transducers, and both pressure and segment length measurements were recorded on a Brush 480 multichannel recorder (Gould, Inc., Instrument Systems Division, Cleveland, Ohio). The peak first derivative of rise in left ventricular pressure (dP/dt) was obtained electronically.

Postextrasystolic measurements: In all dogs, right ventricular pacing was performed at a constant rate of 128 ± 3 beats/min. Both before and during ischemia, a single closely coupled electric stimulus (3 msec duration, 5 to 7 milliamperes amplitude) was introduced by way of the right ventricular pacing electrode in the cardiac cycle immediately after emergence from the refractory period, at a fixed coupling interval of 179 ± 3 msec after the preceding R wave. The pulse stimulator was designed with special gating circuitry to produce a complete compensatory pause, thereby allowing maximal postextrasystolic potentiation to ensue. After control measurements were obtained, the coronary artery was occluded for 10 minutes. Postextrasystolic potentiation was intermittently assessed with serial measurements performed at 30 second intervals throughout the period of ischemia.

Arterial carbon dioxide and oxygen tensions, pH, hematocrit and body temperature were maintained within normal physiologic ranges.

Data analysis and calculations: Phasic recordings of segment length from all three zones before and during ischemia were simultaneously compared with the effects of postextrasystolic potentiation (Fig. 2). An index of regional segment work was obtained by plotting instantaneous left ventricular pressure versus segment length simultaneously

* Border zone segment length placement was determined by occluding the left anterior descending coronary artery for 10 to 15 seconds to define the gross margins of cyanosis induced by the transient interruption of coronary flow. After release of the ligature, the gauge was positioned along the perimeter of the cyanotic border. Studies in this laboratory have confirmed the accuracy of this marginal zone by regional myocardial blood flow and histochemical staining with tetrazolium blue in dogs subjected to 4 hours of ischemia (unpublished observation).

TABLE I

Hemodynamic Data Before and After Occlusion of the Left Anterior Descending Coronary Artery (mean ± standard error of the mean)

Condition	Mean Aortic Pressure (mm Hg)	Left Ventricular End-Diastolic Pressure (mm Hg)	Peak dP/dt (mm Hg/sec)
Control	110 ± 2	9 ± 1	3631 ± 236
30 seconds	104 ± 3	11 ± 1	3527 ± 214
1 minute	108 ± 3	12 ± 2	3375 ± 277
2 minutes	107 ± 2	13 ± 2*	3061 ± 287*
5 minutes	107 ± 2	13 ± 1*	3076 ± 229*
10 minutes	103 ± 3	13 ± 1*	3055 ± 242*

* Probability $P < 0.05$ compared with control state.

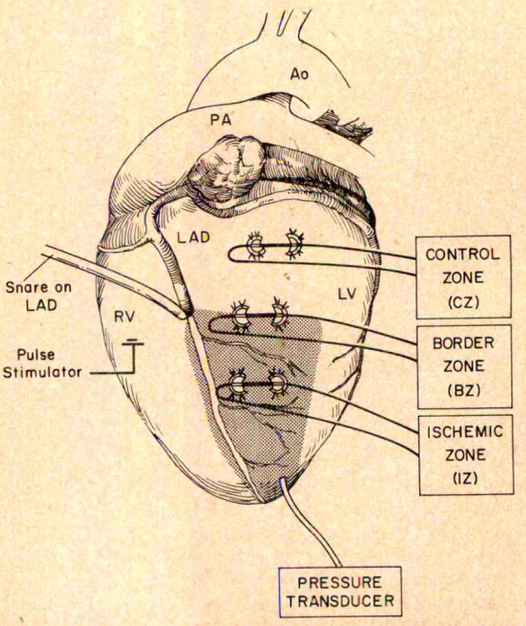

FIGURE 1. Schematic drawing of the anterior surface of the canine left ventricle illustrating the site of attachment of epicardial segment length gauges in the central ischemic zone (IZ), border zone (BZ), and control zone (CZ). Ischemia was induced by tightening the snare of the left anterior descending coronary artery (LAD). Pressure was measured with a short catheter attached directly to a strain gauge and inserted through the left ventricular apex. A bipolar pacing electrode, sutured to the right ventricle (RV), is also shown. Ao = aorta; LV = left ventricle; PA = pulmonary artery.

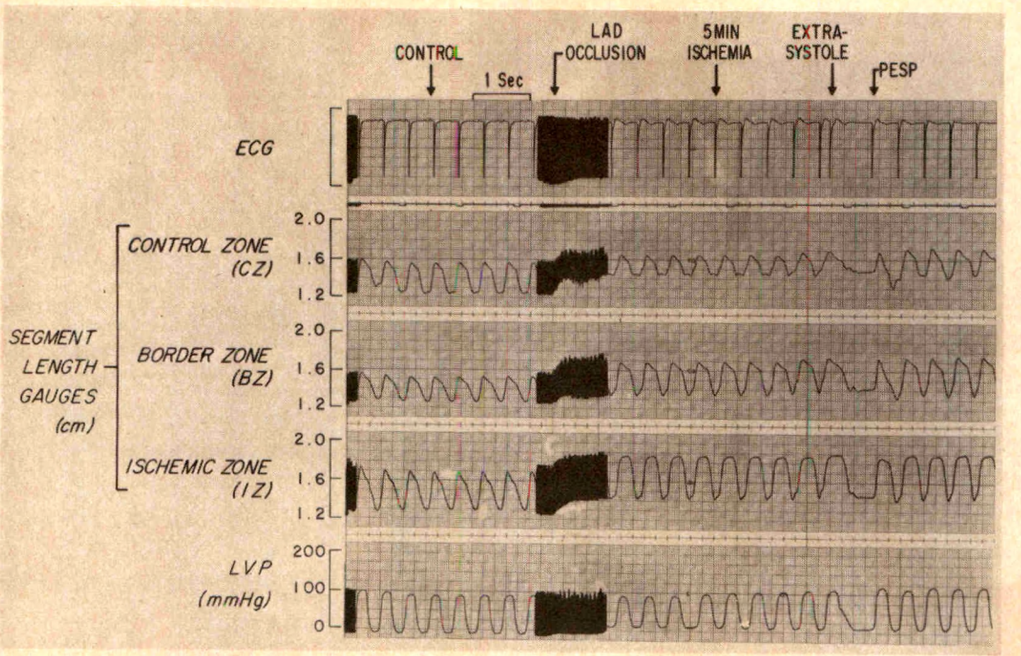

FIGURE 2. Phasic recordings during the control period (before ischemia) and at 5 minutes of ischemia after occlusion of the left anterior descending coronary artery (LAD) in a typical experiment. **From the top down** are depicted the electrocardiogram (ECG), epicardial segment length tracings in the control zone (CZ), border zone (BZ) and central ischemic zone (IZ), respectively, and left ventricular pressure (LVP). **Left,** there is normal systolic shortening and diastolic lengthening in all three myocardial segments during the control period. After coronary occlusion **(right),** there is an abrupt change in the contractile pattern in the ischemic zone, with a marked increase in phasic segment length amplitude and end-diastolic segment length. At 5 minutes of ischemia, holosystolic aneurysmal bulging is evident in the ischemic zone as a rounded systolic contour. Border zone segment length tracings show similar changes in phasic segment length amplitude and end-diastolic segment length, but these are less profound than those of the central ischemic zone. At the top of the electrocardiogram on the right, a single closely coupled extrasystole is shown, with the resultant postextrasystolic potentiation response. The effect of postextrasystolic potentiation (PESP) can be seen in each of the three segment length tracings, most notably in the border and ischemic zones, where the marked increase in downward slope during systolic ejection indicates the return of active systolic shortening during acute ischemia.

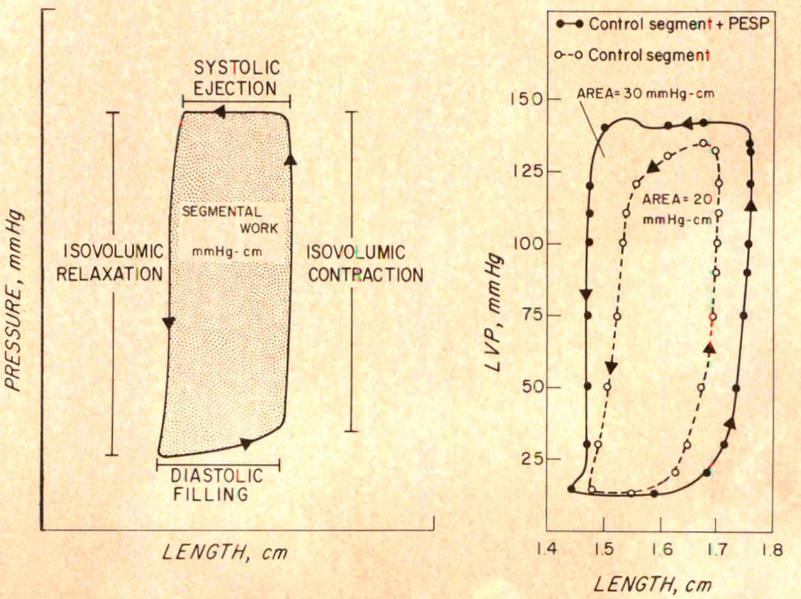

FIGURE 3. Left, schematic illustration of an idealized pressure-length loop of a normal myocardial segment throughout a cardiac cycle. Area within the pressure-length loop is expressed in mm Hg-cm. **Right,** an actual pressure-length loop in a control segment **(open circles),** with a superimposed pressure-length loop obtained in the same control segment with postextrasystolic potentiation **(closed circles).** Note the marked increase in pressure-length loop area with postextrasystolic potentiation (PESP). Length = actual epicardial segment length throughout one cardiac cycle; LVP = left ventricular pressure. **Arrow** shows direction of loop inscription.

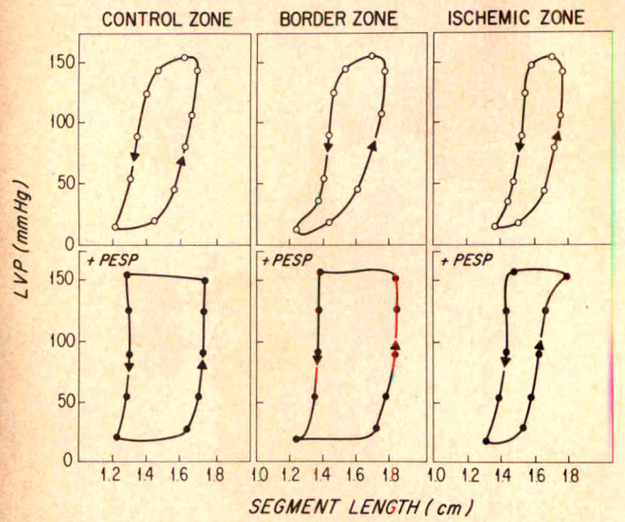

FIGURE 4. Pressure-length loops in the three myocardial segments before ischemia in one experiment. **Top panel (from left to right):** control zone (CZ), border zone (BZ) and ischemic zone (IZ). **Bottom panel,** the potentiated contractile state due to postextrasystolic potentiation (+PESP) in the same three zones. All loops are counterclockwise in orientation, indicative of working myocardial segments. Note the marked increase in loop area with postextrasystolic potentiation in all three zones. LVP = left ventricular pressure.

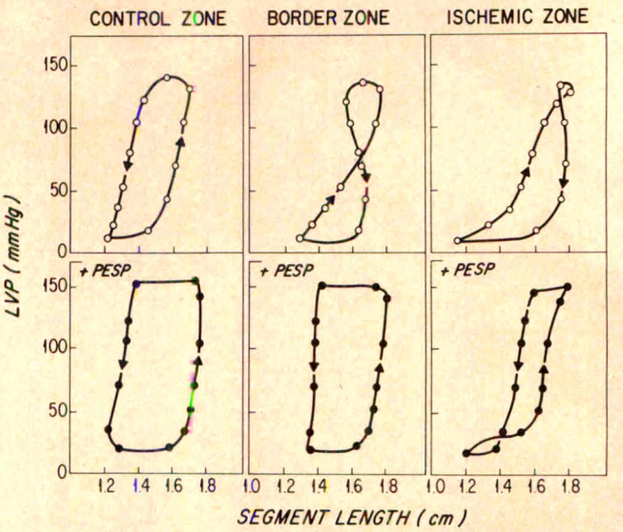

FIGURE 5. Pressure-length loops in the same three myocardial segments as in Figure 4 at 5 minutes of ischemia. The **center frame** of the **top panel** depicts a "figure-of-eight" pressure-length loop in the border zone, indicative of reduced systolic shortening, and paradoxical lengthening during mid and late systole. The center frame of the **bottom panel** shows the response of this regional contraction abnormality to postextrasystolic potentiation. The loop is again fully counterclockwise in orientation and indistinguishable from the border zone segment loop before ischemia. The **right upper panel** shows the pressure-length loop in the central ischemic zone, characterized by holosystolic aneurysmal bulging and illustrated here as a clockwise-oriented loop. The clockwise loop signifies a nonworking myocardial segment. The panel below shows the response of the central ischemic segment to postextrasystolic potentiation, resulting in resumption of systolic shortening, abolition of aneurysmal bulging and a return to a counterclockwise loop. Abbreviations as in Figure 4.

in each of the three myocardial zones—both before and after extrasystoles—to construct pressure-length loops, whose areas were determined with planimetry (Fig. 3). All data are expressed as mean ± standard error of the mean and Student's paired t test was used for statistical analysis.

Results

Hemodynamic changes: The hemodynamic changes that occurred after ligation of the left anterior descending coronary artery (Table I) consisted of a slight but insignificant reduction in mean aortic pressure, a slight but significant increase in left ventricular end-diastolic pressure and a moderate decline in rate of rise of left ventricular pressure (dP/dt) that achieved statistical significance only after 2 minutes.

Ischemic segment function: Figure 2 illustrates the effects of acute coronary occlusion on segment length in the central ischemic, border and control zones in one experiment. Before coronary ligation, phasic recordings of segment length during the cardiac cycle were characterized by normal systolic shortening and diastolic lengthening in all three zones. Characteristically, within seconds after the induction of ischemia, there was a marked increase in the phasic segment length amplitude, and systolic aneurysmal bulging developed in the ischemic segment, as indicated by the rounded systolic contour, during the period of left ventricular ejection. End-diastolic segment length consistently increased after coronary occlusion. The border zone manifested similar changes in both segment systolic shortening and end-diastolic segment length, although they were less profound in degree. In contrast, except for a slight increase in end-diastolic segment length, no significant morphologic segment length changes were observed in normal myocardial segments after coronary occlusion (Fig. 2).

Postextrasystolic potentiation: After the introduction of a single closely coupled extrasystole (Fig. 2), there was marked inotropic augmentation of all three myocardial segments both during the control preischemic state (not shown) and throughout the period of ischemia. In the experiment illustrated in Figure 2, there was resumption of active systolic shortening in both border and ischemic zones with postextrasystolic potentiation.

Figures 4 and 5 illustrate actual pressure-length loops in one experiment obtained, respectively, before and after 5 minutes of ischemia, comparing intrinsic mechanical response with the potentiated contractile state with extrasystoles. All loops in Figure 4 (before ischemia) were counterclockwise in orientation and rectangular in configuration, thus indicating working myocardial segments in all three zones. After 5 minutes of ischemia (Fig. 5), the border zone demonstrated a "figure-of-eight" loop configuration indicative of paradoxical lengthening during mid and late systole, whereas the central ischemic zone was characterized by holosystolic aneurysmal bulging, illustrated as a clockwise loop (nonworking myocar-

dial segment). Despite these regional contraction abnormalities, extrasystoles were capable of producing marked inotropic augmentation with resumption of systolic shortening, abolition of aneurysmal bulging in the ischemic segment and a return to counterclockwise pressure-length loop configuration.

Figure 6 shows that, in all animals throughout the preischemic period and ischemia, the pressure-length loop area in the control zone did not change but increased significantly after extrasystoles. Conversely, within 30 seconds after coronary occlusion, border zone intrinsic mechanical function was reduced by 50 percent and stabilized at that lower level of function throughout the duration of ischemia. However, at each point of comparison throughout ischemia, postextrasystolic potentiation produced significant increases in pressure-length loop area to levels not significantly different from those in the control zone. Ischemic zone segment function deteriorated within seconds after coronary occlusion. The level of intrinsic mechanical dysfunction reached a nadir rapidly and stabilized throughout the period of ischemia but at a lower level than in the border zone. Nevertheless, postextrasystolic potentiation improved segment performance in the ischemic zone, as judged from the consistent increases in pressure-length loop area, throughout the duration of ischemia.

Discussion

This study demonstrates that acutely ischemic myocardium has a considerable latent contractile reserve that can be elicited by postextrasystolic potentiation. The magnitude of the segmental response to extrasystolic potentiation during coronary occlusion was related to location of the segment in the center of the border zone of the ischemic area; postextrasystolic potentiation augmented the border zone to levels of segment function indistinguishable from those found before ischemia, but function in the central ischemic zone was not potentiated completely to normal. The negative values for pressure-length loop area indicate the absence of systolic shortening and the presence of aneurysmal bulging. No residual work was performed by these segments; rather, work was done upon the segments, as illustrated by the clockwise loops. However, despite the absence of work in the unpotentiated ischemic segment, postextrasystolic potentiation consistently augmented regional function significantly for up to 10 minutes of ischemia.

Loss of contractile behavior is the earliest detectable change in ischemic myocardium, and one of the slowest functions to return to normal after reperfusion[1,2,15] even when the period of coronary occlusion has been very brief.[16] The development of systolic aneurysmal bulging of the ischemic segment of the left ventricular wall immediately after coronary occlusion has been extensively documented by several investigators[1,2,13,17–20] utilizing various techniques. Similar segment wall motion abnormalities have also been observed in patients after acute myocardial infarction and in some patients with coronary artery disease and myocardial dysfunction.[21–23]

Mechanical performance of ischemic left ventricle: The deterioration of mechanical performance in the acutely ischemic left ventricle is due to a complex interaction of factors: (1) the absolute mass of noncontracting myocardium[24,25]; (2) systolic aneurysmal bulging of the ischemic segment, which diminishes effective stroke volume[2,26]; (3) the contractile response of the nonischemic segments of myocardium[27]; (4) alterations in diastolic compliance in zones of ischemia and infarction[26,28]; and (5) underlying biochemical mechanisms such as intracell acidosis (which may impair calcium ion–troponin interaction) or decreased cell levels of adenosine triphosphate.[29,30] Poor recovery of contractile function after brief periods of ischemia need not indicate that permanent damage to the myocardium has occurred because recovery may occur over a prolonged period of time.[31] Furthermore, both pharmacologic inotropic stimulation and postextrasystolic potentiation can augment contractility after ischemic depression of mechanical function.[2,7–10]

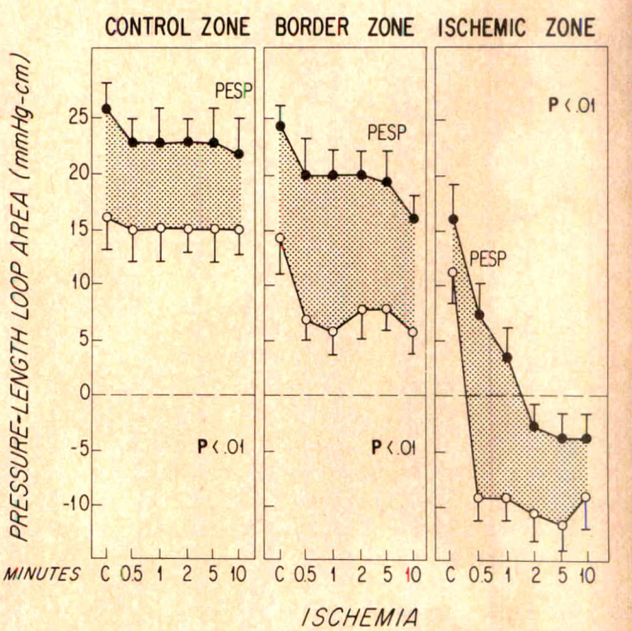

FIGURE 6. Pressure-length loop areas (mean ± standard error of the mean) for the eight dogs, plotted as a function of time throughout 10 minutes of ischemia. The **left panel** depicts control zone intrinsic segment work compared with the postextrasystolic potentiation (PESP)-augmented loop areas in the control period (C) before ischemia and at 30 seconds and 1, 2, 5 and 10 minutes of ischemia, respectively. Postextrasystolic potentiation augmented segment work to significantly higher values ($P < 0.01$, paired Student's t test) at each point. The **center panel** depicts the progression of regional contraction abnormalities in the border zone, compared with the potentiated contractile state with PESP throughout 10 minutes of ischemia. Again, PESP augments depressed border zone intrinsic mechanical function to control values before ischemia at each point of comparison ($P < 0.01$). The **right panel** illustrates the dramatic deterioration of intrinsic mechanical function in the central ischemic zone and the effect of PESP on regional segmental performance throughout 10 minutes of ischemia. Although PESP did not completely augment segment function to normal, loop area increased to significant levels at each point of comparison ($P < 0.01$).

Effect of inotropic stimulation by pharmacologic means: Enhanced mechanical performance after inotropic stimulation has been proposed as a means of detecting residual contractile function. Left ventricular regional contraction abnormalities have been lessened by systemic administration of epinephrine[7] and isoproterenol.[32] However, this effect may not be sustained,[11] presumably because myocardial depression may ensue because of increased oxygen requirements in the absence of augmented coronary flow.[12] Similarly, pharmacologic inotropic stimulation with intracoronary administration of isoproterenol or infusion of calcium may reveal residual contractile function in acutely ischemic myocardium,[8] but a consistent change in total segment shortening may not occur because of late systolic expansion.[2,8] More important, the absence of a response to pharmacologic inotropic agents cannot be used to infer nonviability[2,8,9,33] because postextrasystolic potentiation may augment segment function under similar conditions of acute regional ischemia. Thus pharmacologic stimulation of ischemic cardiac tissue has inherent limitations of interpretation and may result in extension of ischemic injury because of a sustained increase in myocardial oxygen consumption.[25]

Advantages of inotropic stimulation by postextrasystolic potentiation: Inotropic augmentation after the introduction of a single closely coupled extrasystole has been shown in this study and others[8,9] to be a reliable, reproducible and sensitive method of detecting residual contractile function. Postextrasystolic potentiation has several advantages over pharmacologic inotropic interventions: (1) single beat inotropic augmentation, although it may increase energy needs for this single beat, does not produce prolonged secondary myocardial depression because of a sustained increase in oxygen needs; (2) postextrasystolic potentiation is a repeatable and readily controlled means of eliciting a maximal contractile response; and (3) the magnitude of this response is a function of the coupling interval of the preceding beat because the more premature the extrasystole, the greater the subsequent augmentation; thus, by manipulating the coupling interval, a high degree of control may be exerted upon the degree of augmentation in the subsequent beat. In this study, several coupling intervals were utilized in each dog before coronary occlusion to determine the optimal coupling interval for that experiment; that is, the shortest coupling interval that could produce ventricular capture was chosen to elicit the maximal postextrasystolic potentiation of all segments. This optimal coupling interval was used throughout the duration of ischemia at the same paced heart rate.

Pressure-length loops as index of regional segment function: This study further demonstrates the utility of pressure-length loops as an index of regional segment function, as shown previously during acute ischemia.[13,14] Although we cannot discount the possibility that loop configuration may be influenced by the degree of passive stretch and by phase differences between ischemic and normal myocardium, we believe that the improvement of loop configuration in border and ischemic zones with postextrasystolic potentiation reflects an improvement in segment performance. In addition, because the period of ischemia was too short to produce myocardial necrosis, no definite conclusions about latent viability of ischemic segments in established myocardial infarction can be inferred from our data. Rather, our findings suggest that wall motion abnormalities may be reversed with postextrasystolic potentiation during brief periods of coronary occlusion.

Clinical implications of study: These deserve comment. First, the exact mechanism responsible for the immediate deterioration in contractility during ischemia has not yet been elucidated. One current hypothesis is that intracell acidosis consequent to ischemia interrupts the contractile process by inhibiting the calcium ion interaction with troponin,[29,30] or other sites in the excitation-contraction coupling mechanism.[34] An ischemia-induced reduction in the slow inward calcium ion current could theoretically rapidly diminish contractility.[35] Alternatively, depressed cell levels of adenosine triphosphate and disruption of high energy phosphate bonds have been postulated as a possible pathogenetic factor in the rapid decrease in contractility during ischemia.[36,37] Although our results do not allow us to speculate about the possible mechanisms for the rapid deterioration in myocardial contractility during coronary occlusion, they indicate that early "pump failure" of the ischemic myocardium is related to an inhibition of the calcium ion-mediated excitation-coupling mechanism of contraction, and that the reversal of regional mechanical dysfunction with postextrasystolic potentiation up to 10 minutes after acute coronary occlusion may be attributable to enhanced calcium ion influx produced by closely coupled extrasystoles.[38]

Second, our study suggests that postextrasystolic potentiation may identify a potential contractile reserve in both border and ischemic zones during brief periods of coronary occlusion. The concept of limiting myocardial infarct size has attained considerable importance in recent years. Thus, there have been many therapeutic interventions aimed largely at the population of cells in the border zones of ischemia surrounding central zones of infarction, where minor modifications in oxygen requirements, oxygen supply or availability of substrate might be critical in determining whether the cells ultimately survive. The magnitude of the border zone of ischemia may be considerable. Radioautographic techniques employed to study ischemic flow profiles have demonstrated that as much as one third of the entire zone of ischemia may comprise areas in which flow is reduced below normal but not to the low levels found in the central infarct zone.[39] Similar electrocardiographic and mechanical correlates have been described[20,39,40] to suggest that substantial zones of myocardium may be critically compromised but not irreversibly injured, by flow reduction. Our study and others[20,31] have demonstrated that border zones adja-

cent to central zones of intense ischemia show intermediate degrees of contractile impairment.

The confirmation that flow within the center and margins of an experimental lesion is not homogeneous[39–43] forms a conceptual basis for viewing ischemic lesions in patients as representing focal, patchy ischemic processes, analogous to experimental border zones of ischemia, which comprise marginally injured cells. Application of interventions that may influence the function or preservation of these marginal cells may represent the most effective approach to the study of protecting ischemic myocardium. Our findings indicate that the mechanical performance of border zone ischemic myocardium can be augmented inotropically to control levels with postextrasystolic potentiation. These experiments suggest that (1) wall motion abnormalities during brief periods of ischemia, such as those seen in unstable angina, may be amenable to coronary revascularization; and (2) systematic utilization of single closely coupled extrasystoles may provide a useful means of assessing preservation of regional mechanical performance during intervention therapy.

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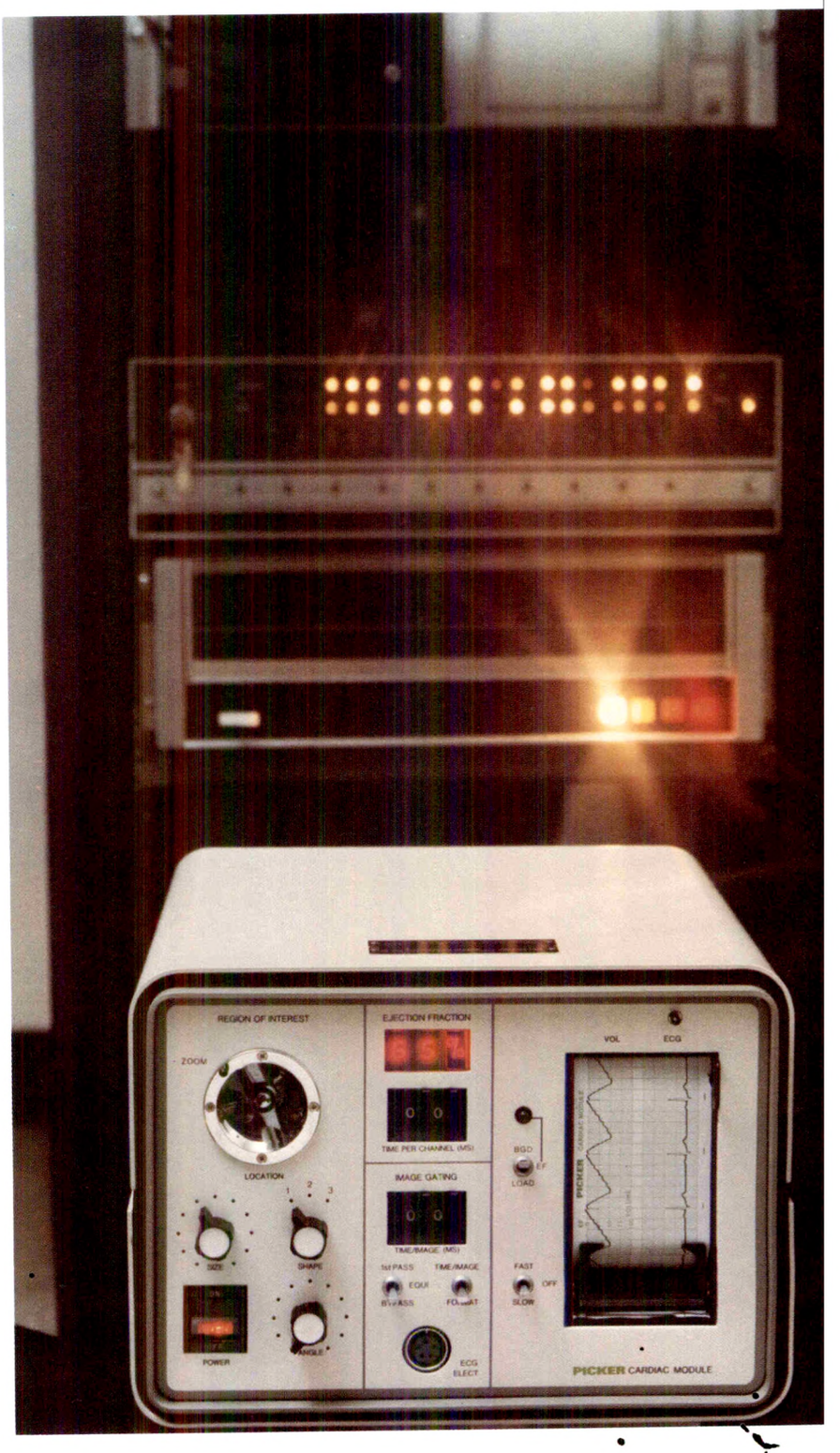

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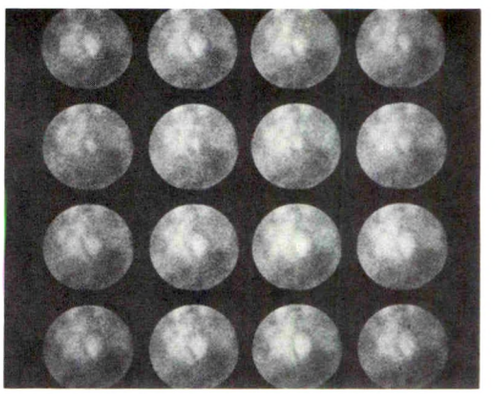

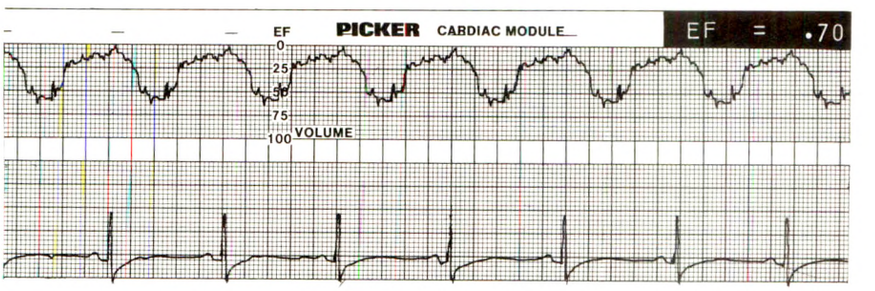

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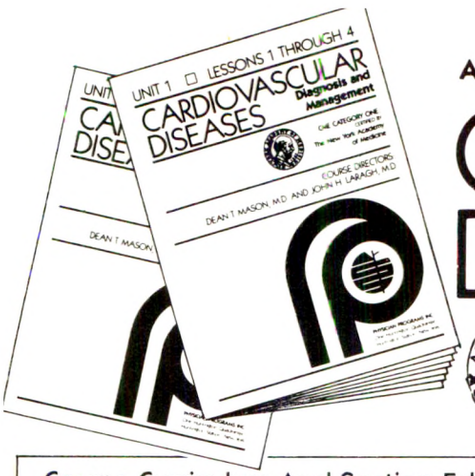

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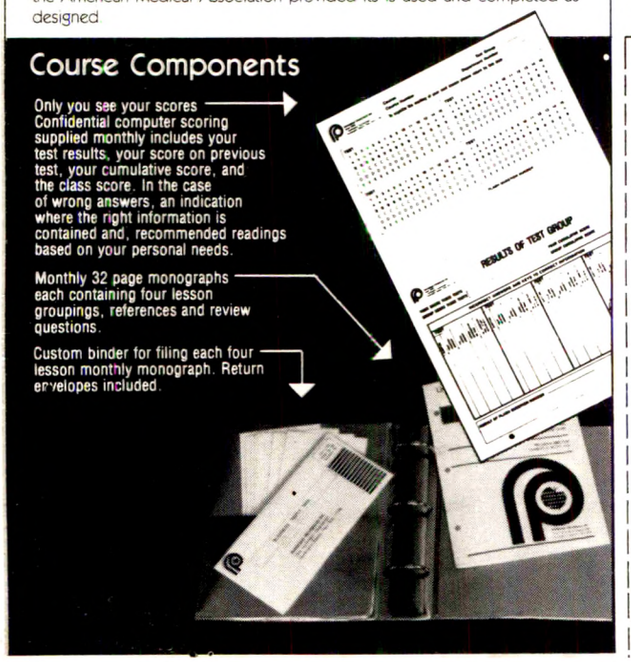

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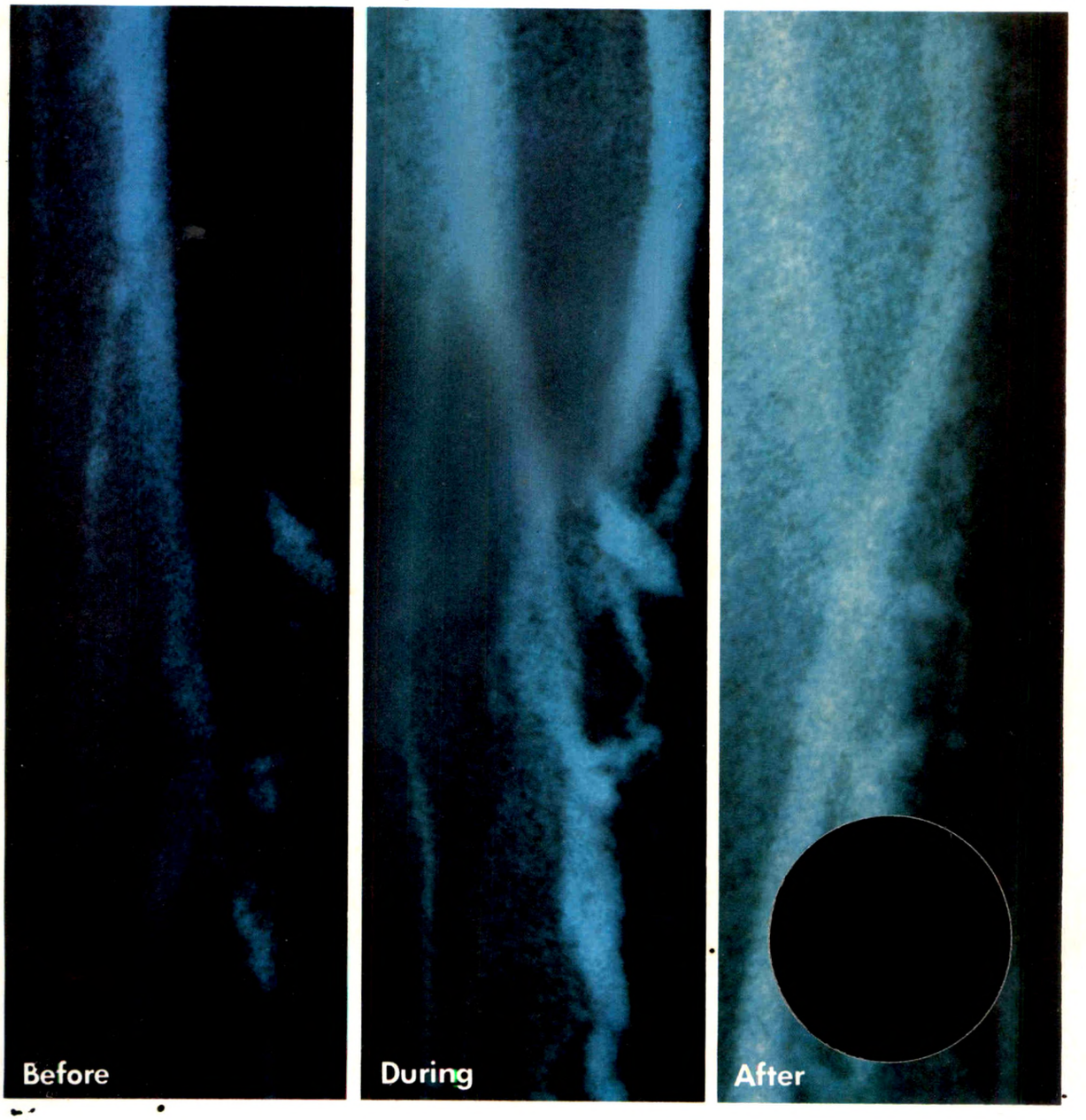

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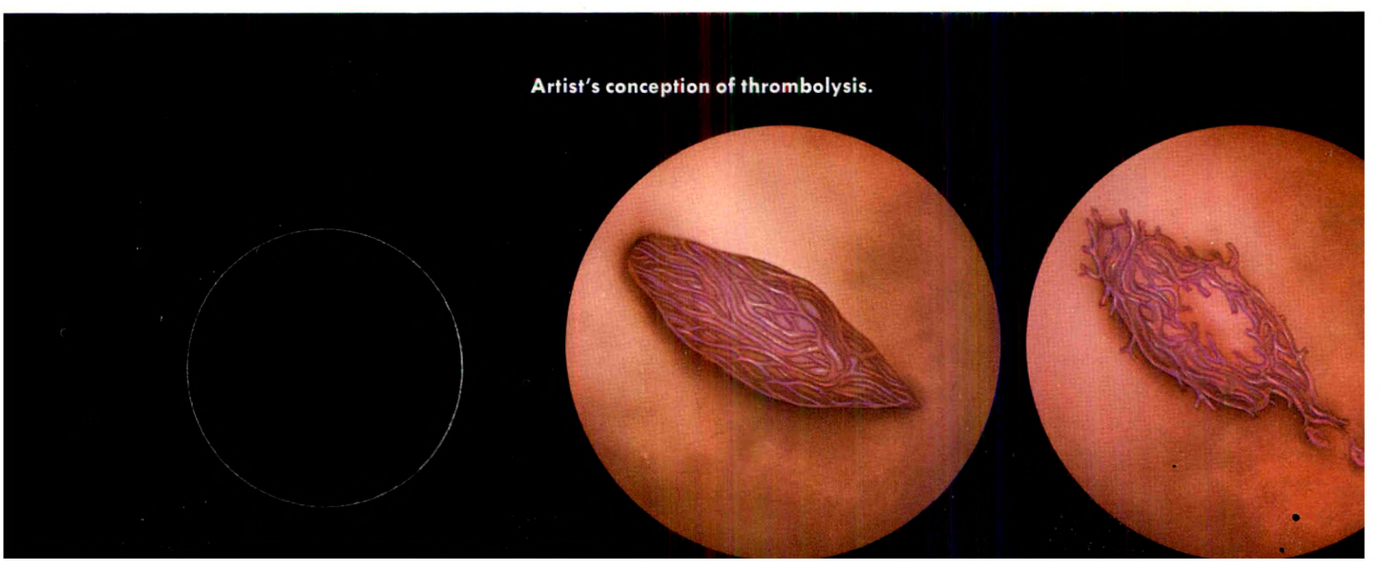
Streptase®
(streptokinase) I.V.

Now... a new alternative to surgery...

- **avoids the risks associated with thrombectomy.**
- **reduces the need for high-risk pulmonary embolectomy.**



To lyse venous thrombi and pulmonary emboli—intravenous Streptase®(streptokinase). Anticoagulant therapy is given following Streptase to prevent rethrombosis.

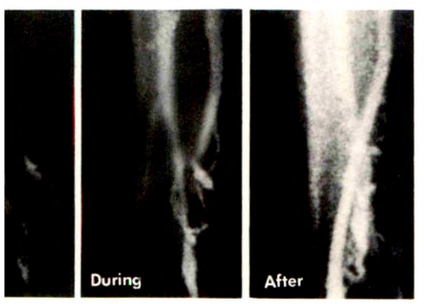
Now physicians have available a medical therapy for the early clearance of deep venous thrombi that is preferable to thrombectomy because it may preserve valvular function and avoid chronic stasis, although long-term benefits have not been established. And acute massive pulmonary emboli may be cleared without high-risk embolectomy.

A unique mode of action

New Streptase is the highly purified form of streptokinase, a bacterial protein derived from β-hemolytic streptococci. It combines with plasminogen to form an activator complex that converts residual plasminogen into the proteolytic enzyme plasmin. Plasmin hydrolyzes fibrin into polypeptides.

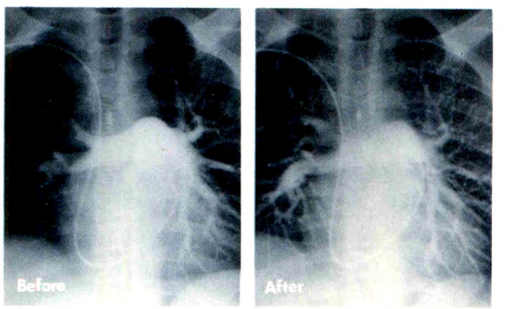
High rate of clinical success demonstrated by angiography:

In patients with venous thrombosis



In comparative controlled studies of 78 patients with venous thrombosis, Streptase produced complete or significant clearing of the thrombosis in 54% of patients while only 7% on conventional heparin therapy showed similar results.

In patients with pulmonary embolism



In studies of 124 patients with pulmonary embolism, complete or significant clearing was seen in 66% of the patients on Streptase but in only 11% of the heparin-treated patients.

Table I
Comparative angiographic results during controlled investigations*

Results	Venous Thrombosis		Pulmonary Embolism	
	Streptase (37 patients)	Heparin (41 patients)	Streptase (36 patients)	Heparin (88 patients)
Complete clearing	22%	5%	22%	5%
Significant, but incomplete, clearing	32%	2%	44%	6%
Minimal clearing	21%	20%	20%	43%
No change	22%	66%	14%	35%
Worse	3%	7%	0%	11%

In most cases, clearance was achieved in 72 hours or less.

For best results, Streptase should be used within 2 weeks after onset of venous thrombosis symptoms and within 5 days after onset of pulmonary embolism symptoms. Please see last page of this advertisement for a brief summary of prescribing information.

*Data on file and available on request from Hoechst-Roussel Pharmaceuticals Incorporated. Pulmonary embolism data include those taken from National Heart and Lung Institute study.

Thrombosis and thrombolysis information available

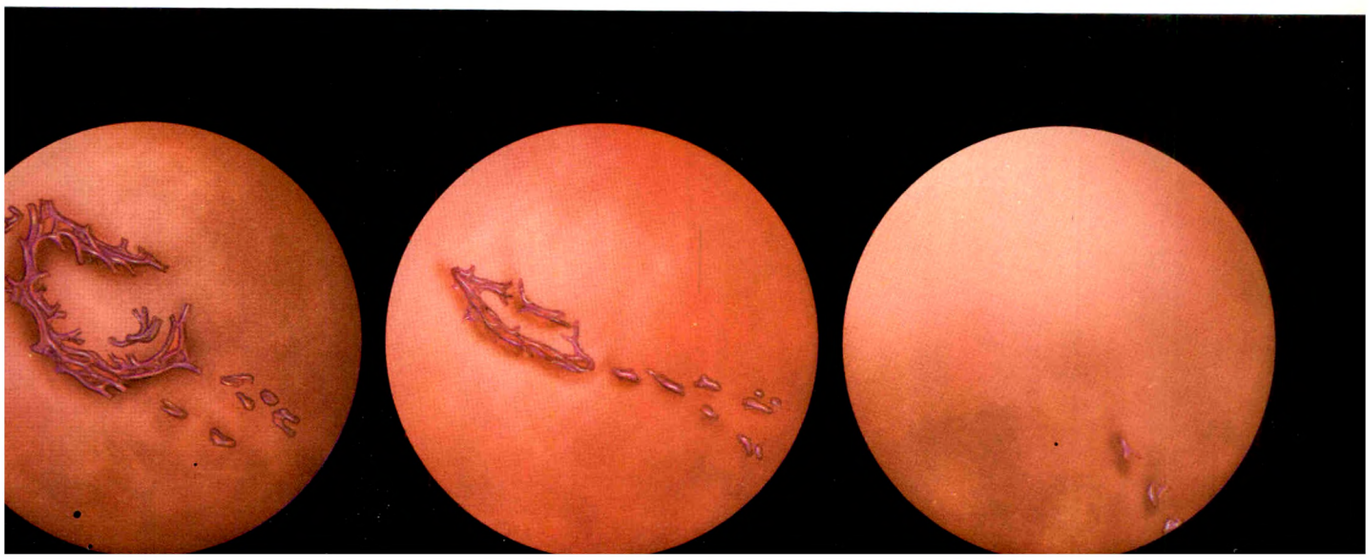
When considering the use of Streptase (streptokinase), comprehensive knowledge of prescribing information and strict observance of the contraindications, warnings, precautions, and dosage and administration instructions are most important to minimize the incidence and severity of adverse reactions, the most significant and frequent being fever, allergy and bleeding. Use of Streptase requires an interdisciplinary effort and therefore should be reserved for those hospitals with facilities for angiography, coagulation testing and volumetric or syringe pump administration of Streptase intravenously.

Hoechst-Roussel has prepared a comprehensive educational program on thrombosis and thrombolysis that includes two films, associated monographs, dosage and administration guidelines and a Speakers Bureau of physicians experienced in the use of thrombolytic therapy.

For information, interested physicians may contact Scientific Services, Room 236, Building M, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876, (201) 685-2611, or the local Hoechst-Roussel Sales Representative.

For a complete list of indications, contraindications, warnings, precautions, adverse reactions and dosage information, please refer to the full prescribing information for Streptase, a summary of which appears on the following page.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876



Streptase®
(streptokinase) I.V.

Brief Summary of the Prescribing Information

Streptase® (streptokinase) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring can be performed. The full prescribing information should be read for complete details.

When considering treatment with Streptase® (streptokinase) the overall clinical status and history of the patient should be carefully assessed. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with Streptase® (streptokinase) therapy than with heparin or oral coumarin compound anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient should be weighed against the potential benefits of treating the patient with Streptase® (streptokinase).

Indications

Pulmonary Embolism: Streptase® (streptokinase) is indicated in adults for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels. It may also be indicated for embolization accompanied by unstable hemodynamics. The diagnosis should be confirmed by objective means. Streptase® (streptokinase) treatment should be instituted as soon as possible after onset of symptoms and no later than five days after onset. Reduction of morbidity or mortality has not been established.

Deep Vein Thrombosis: Streptase® (streptokinase) is indicated for lysis of acute, extensive thrombi of the deep veins in adults. Diagnosis should be confirmed by objective methods.

Streptase® (streptokinase) should be administered as soon as possible after the onset of the thrombotic event (preferably within several days), although slight enhancement of clot lysis has been shown with initiation of therapy up to two weeks after the onset of symptoms.

Contraindications

Predisposition to Bleeding: Because thrombolytic therapy increases the risk of bleeding, Streptase® (streptokinase) is contraindicated when the following conditions exist: surgery within 10 days, liver or kidney biopsy within 10 days, intraarterial diagnostic procedure within 10 days, ulcerative wound, recent trauma, visceral carcinoma, parturition (within 10 days), ulcerative colitis or diverticulitis, hypertension, liver or kidney disease, thrombocytopenia or other evidence of defective hemostasis, active tuberculosis, subacute bacterial endocarditis, gastrointestinal bleeding within 6 months.

Predisposition to Allergy: Streptase® (streptokinase) is contraindicated in patients with a history of a previous severe allergic reaction to Streptase® (streptokinase) or who present a significant risk of an allergic response.

Recent Cerebral Embolism, Thrombosis, or Hemorrhage: Treatment with Streptase® (streptokinase) is contraindicated for at least two months.

Predisposition to Systemic Infection: Use of Streptase® (streptokinase) in septic thrombophlebitis may be hazardous because of the risk of inducing systemic infection.

Warnings

Bleeding: Activation of the fibrinolytic system with Streptase® (streptokinase) results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy. Although the aim of Streptase® (streptokinase) therapy is the production of sufficient amounts of plasmin for lysis of intravascular deposits of fibrin, other fibrin deposits are also destined for lysis and bleeding may result. The possibility of bruising or hematoma formation especially with intramuscular injections is high.

Bleeding at sites of recent invasive procedures may occur. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. Also, invasive venous procedures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observations.

Spontaneous bleeding from internal sites may also occur.

Should serious spontaneous bleeding occur, the infusion of Streptase® (streptokinase) should be terminated immediately.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. These products possess an anticoagulant effect and should be monitored by serial thrombin time determinations.

Predisposition to Cerebral Embolism: Treatment with Streptase® (streptokinase) of patients with conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Allergy: Streptase® (streptokinase) is antigenic, thus, allergic reactions including anaphylaxis may occur.

Recipients of Streptase® (streptokinase) should be observed carefully during the first few hours of therapy. Patients with known allergies to other antigens are more likely to react. If significant changes in blood pressure or asthmatic symptoms occur which might be due to allergy, the infusion should be terminated and symptomatic treatment employed.

Other mild allergic manifestations have also been observed but generally are not serious enough to require discontinuation of therapy.

Use of Anticoagulants: Concurrent use of anticoagulants with Streptase® (streptokinase) is not recommended and may be hazardous. A thrombin time of less than twice the normal control value is adequate for starting Streptase® (streptokinase) infusions safely following the use of heparin. Heparin should not be started following Streptase® (streptokinase) therapy until the thrombin time has returned to less than twice the normal control value.

In order to minimize rethrombosis, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following Streptase® (streptokinase) therapy.

Use in Pregnancy and in Children: Streptase® (streptokinase) therapy during pregnancy and in children is not recommended.

Precautions

If the patient's history gives rise to suspicion of elevated resistance, the streptokinase resistance test should be used to determine the proper loading dose. When resistance levels in excess of 1,000,000 I.U. are found, Streptase® (streptokinase) should not be administered.

Streptase® (streptokinase) infusions have been associated with altered platelet function. Concurrent use of drugs that may potentiate this effect should be avoided.

Adverse Reactions

Incidence and Management

Bleeding: Severe spontaneous bleeding has been documented in 6 of 292 patients during Streptase® (streptokinase) treatment. Several fatalities due to cerebral hemorrhage have occurred during Streptase® (streptokinase) therapy. Less severe spontaneous bleeding has been observed during Streptase® (streptokinase) treatment at approximately twice the frequency as that occurring during heparin therapy. In several instances, spontaneous bleeding has been traced to concomitant anticoagulant treatment which is not recommended.

Management of Severe Bleeding: Streptase® (streptokinase) therapy must be discontinued. I very rapid reversal of the fibrinolytic state is required, treatment with aminocaproic acid (EACA) can be instituted.

Plasma volume expanders are indicated to replace blood volume deficit. If blood loss has been large, Red Blood Cells (Human) may also be indicated. If only Whole Blood (Human) is available, it may also be used.

Allergic Reaction

Incidence: Reactions determined to represent possible anaphylaxis have been observed in 7 of 292 patients treated with Streptase® (streptokinase). These ranged in severity from minor breathing difficulty to bronchospasm, periorbita swelling, or angioneurotic edema. Other milder allergic effects have been observed in approximately 12% of patients. There was no apparen relationship to dosage.

Management of Allergic Reactions: Mild and moderate reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase® (streptokinase), with corticosteroids administered intravenously as required.

Fever

Incidence: One-third of patients treated with Streptase® (streptokinase) have shown increases in body temperature of 1.5°F or more; the incidence of fever ≥104°F was 3.4%.

Management: Symptomatic treatment is usuall sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

Phlebitis: Phlebitis near the site of intravenous infusion of Streptase® (streptokinase) has occurred in less than 2% of patients.

How Supplied

Streptase® (streptokinase) is supplied as a lyophilized white powder in 6.5 ml vials (in packages of 10) with color-coded labels corresponding to the amount of purified Streptase® (streptokinase) in each vial as follows: 100,000 IU (yellow), 250,000 IU (green), 750,000 IU (bl

In each vial there is a 20% overfill above tha stated on the label. Each vial also contains 25 mg cross-linked gelatin polypeptides and 25 mg sodium L-glutamate as stabilizers.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876

REG TM HOECHST AG

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Hoechst-Roussel Pharmaceuticals Incorporated
Manufactured by Behringwerke AG
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WHAT TO LOOK FOR IN A CATHETER INTRODUCER SET

This is the UMI Sterile Percutaneous Catheter Introducer, available in sizes 4F to 9F. Using it, you can introduce balloon "floating" catheters, closed-end catheters, or electrode probes with great ease, thereby minimizing trauma to the patient. It is carefully thought out in design and engineering, and manufactured to our high quality standards. Here are its main features:

1. CLOSE FIT. Each component is matched with precision to its neighbor. They move freely but firmly in contact with each other.

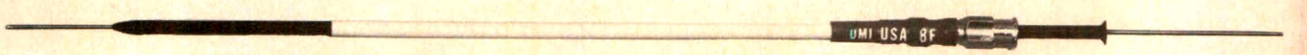
2. THE SHEATH IS TAPERED. For greater ease of introduction, the distal tip is tapered for a closer fit with the dilator. This is an exclusive UMI feature.

3. THE SHEATH IS THIN YET STRONG. Its wall is only .007" thick. Yet there is less chance it will "accordion" passing through tissue. Both it and the dilator are made of special Teflon.®

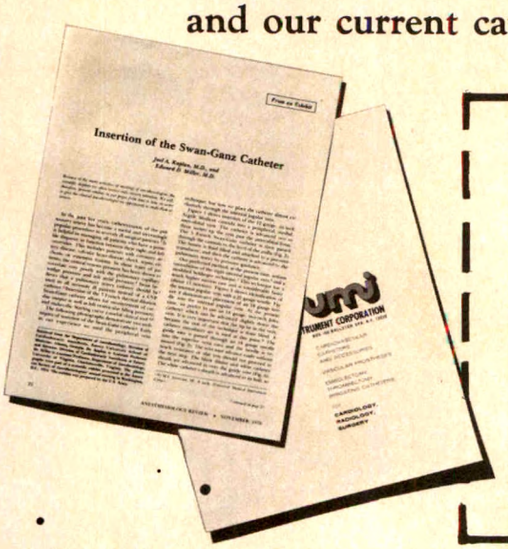
4. THE DILATOR'S DISTAL TAPER is uniform and gradual, meeting the guide wire closely for ease of introduction.

5. THE DILATOR'S FLARE is pronounced — so that it will not enter the sheath.

6. THE GUIDE WIRE is stainless steel, manufactured to close tolerances to assure uniformity.



Although we are a small, young company, UMI already produces catheters and catheter accessories in a great number of sizes and configurations. And we will custom-make to your specifications and needs. To learn more about what we can do for you, please send for a recent reprint from *Anesthesiology Review* and our current catalog.



umi

UNIVERSAL MEDICAL INSTRUMENT CORP.

Dept. 2038, Box 100, Ballston Spa, N.Y. 12020

Name of Physician or Technician _____

Hospital _____

Department _____

Hospital Address (Street) _____

City _____ State _____ Zip _____

A59

That idea, of course, was to record 24 hours of heart activity while the patient followed his daily routine. Holter also introduced a method of reviewing, at high speed on a CRT, the large amount of information thus gathered.

Since then, technical developments have allowed us to extend this idea to a more valuable diagnostic tool. Working with computers, we have been able to get much more out of the recorded data — and get it more reliably.

A good example is the graphic summaries of ectopic activity which are a part of our LCG Report. Neither an examiner nor a computer alone could feasibly provide this kind of graphic information to the physician. Together they provide it accurately and reliably.

In this exclusive Clinical Data procedure, the computer displays detected ectopic events to the examiner for validation and quantitation. Then the computer prints out, for each focus, a graphic summary of the frequency per hour of ectopic activity, and a quantitation of the number of singles, pairs, and runs that occurred for each focus during each hour of the recording.

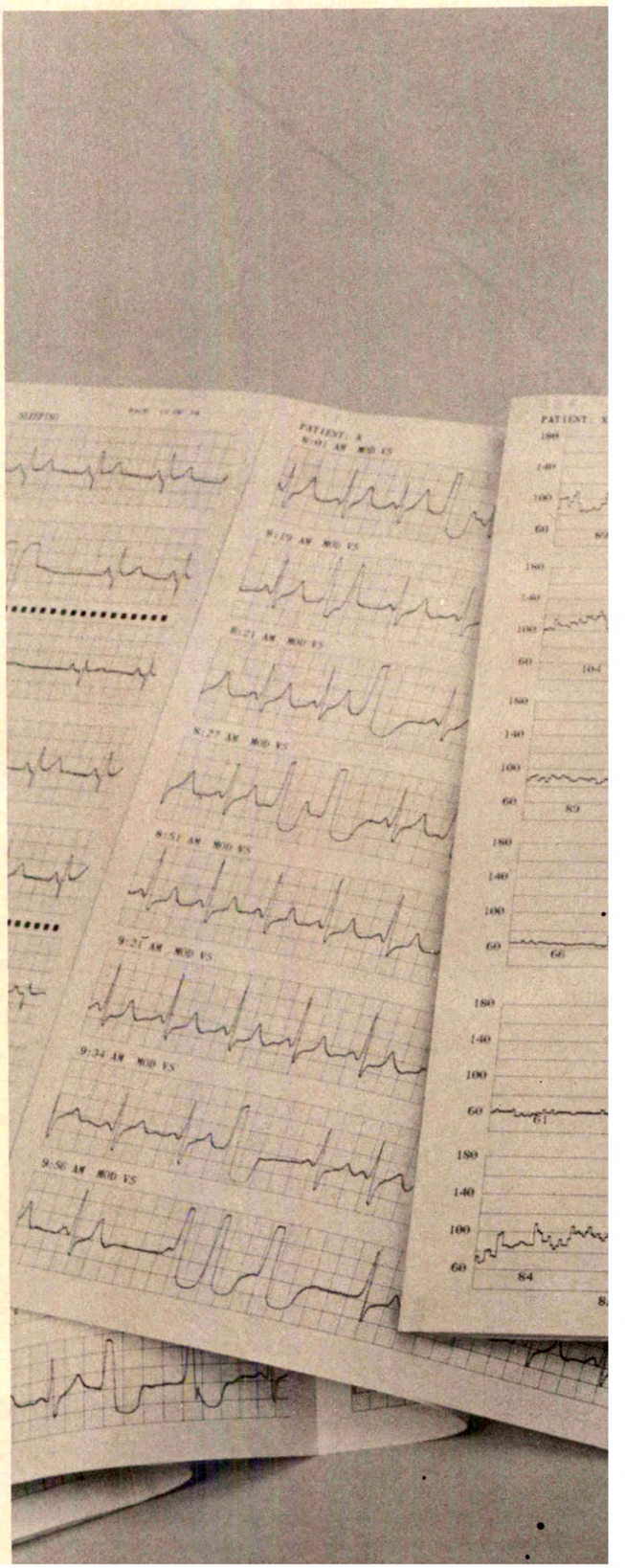
LCG means service, too. We provide the optimum number of recorders you may need, and we maintain, replace or update them. Turn-around-time is short, often 24 hours. But before any report is delivered, it is reviewed by our supervising RN's.

A lot has happened since 1961. Let us bring you up to date with the complete LCG story, including a sample Report.

Clinical Data, Inc., 1371 Beacon Street, Brookline, Mass. 02146. Telephone toll free 1-800-225-9180.

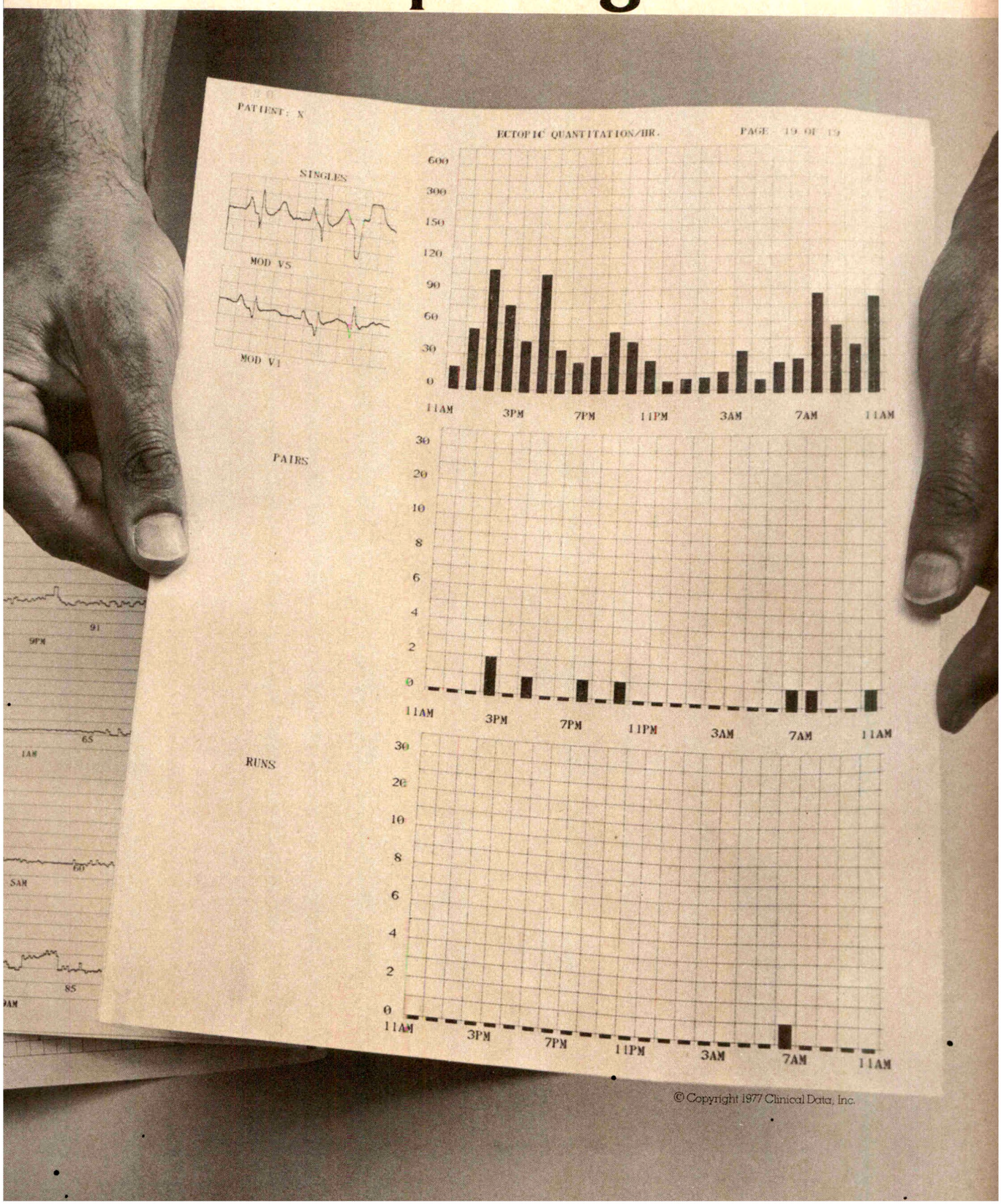
Clinical Data, Inc.

Accurate Data, Clearly Reported



The Clinical Data ECG:

It brings Holter's idea into the computer age.



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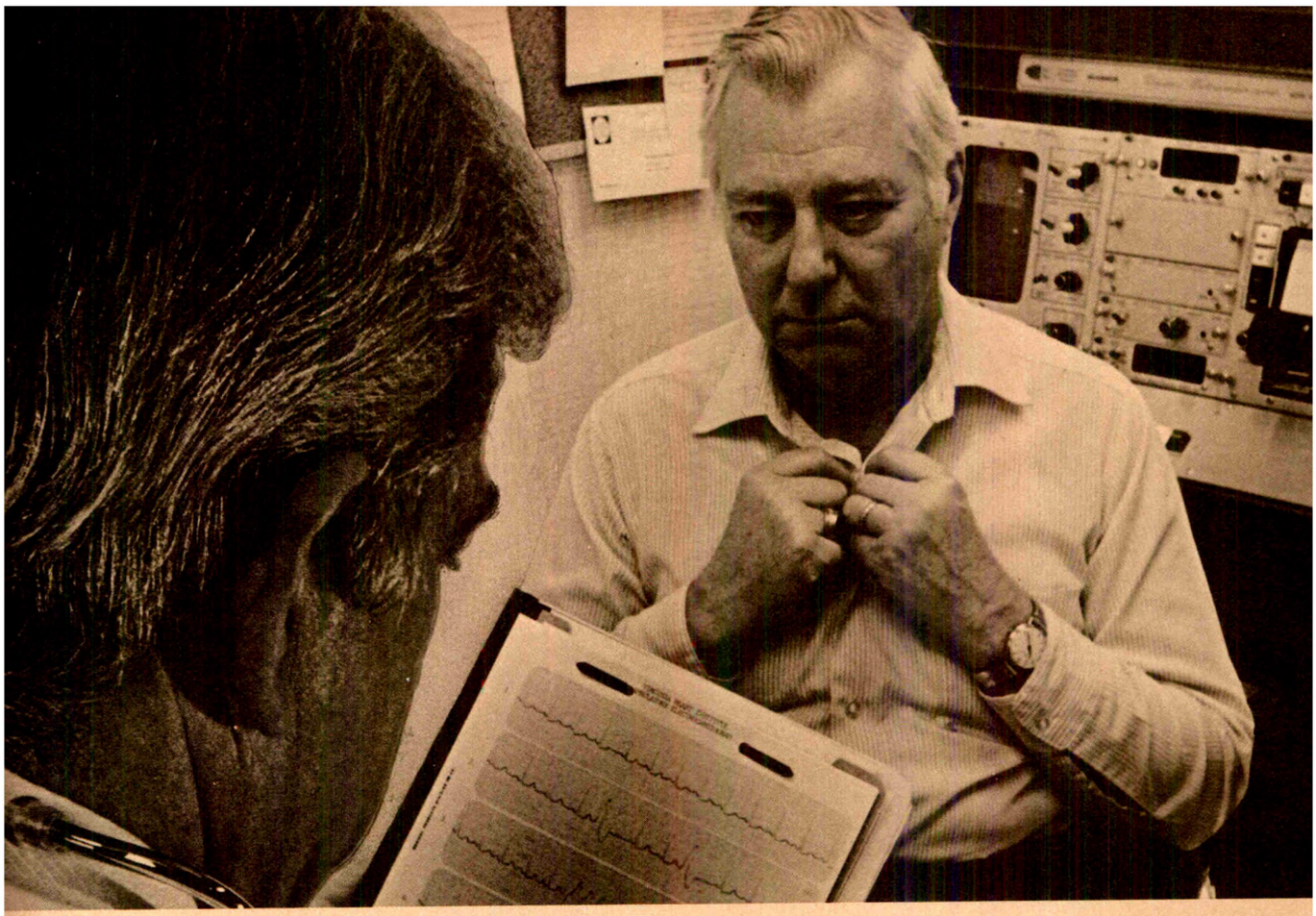
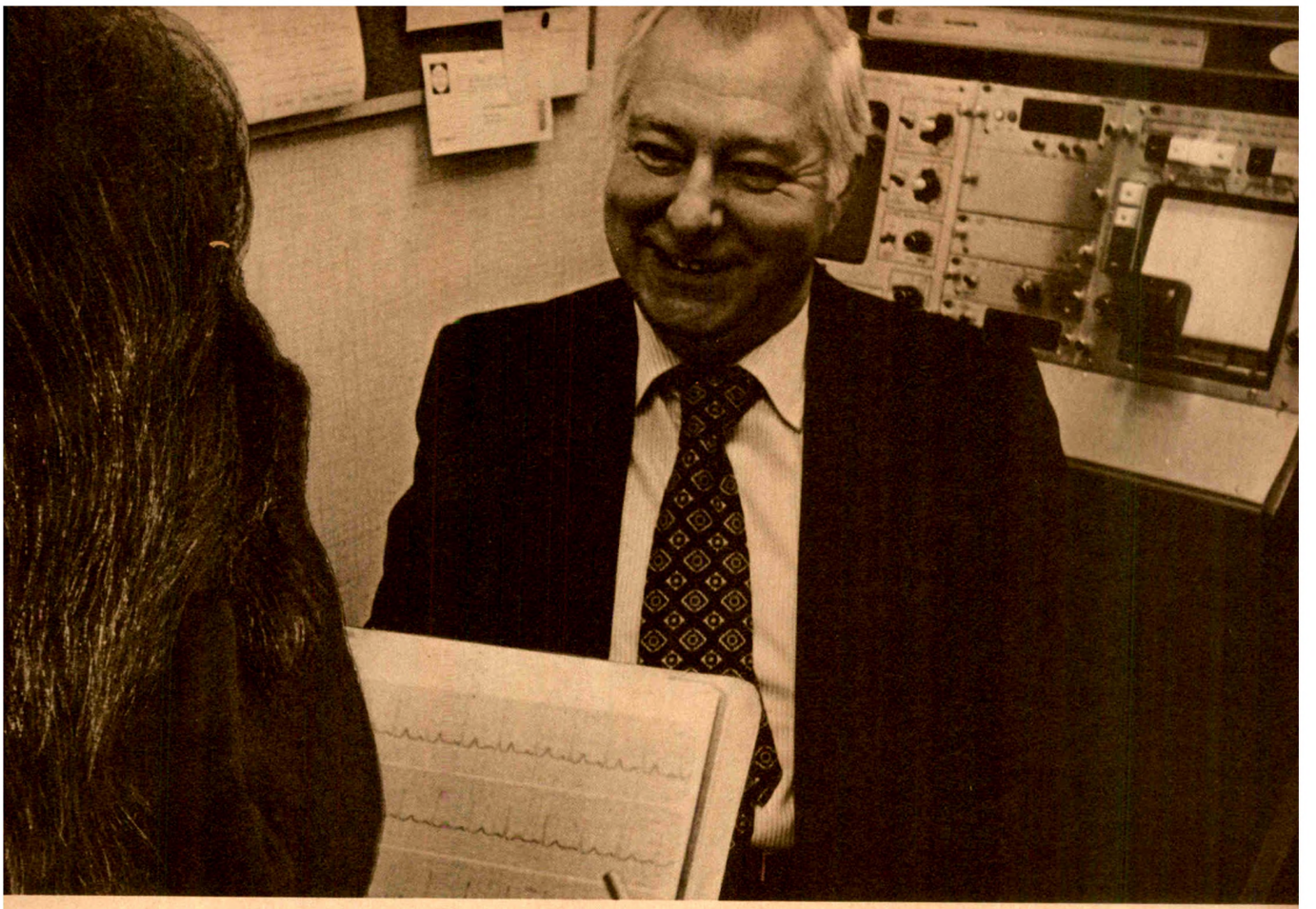


Diagnosis: PVC's
(Premature Ventricular Contractions)

initial therapy:
quinidine sulfate tablets
at
9 a.m.
1 p.m.
5 p.m.
9 p.m.



Then, for convenience and compliance... a welcome change- simple q 8-12 hour dosage

Quinidex Extentabs®

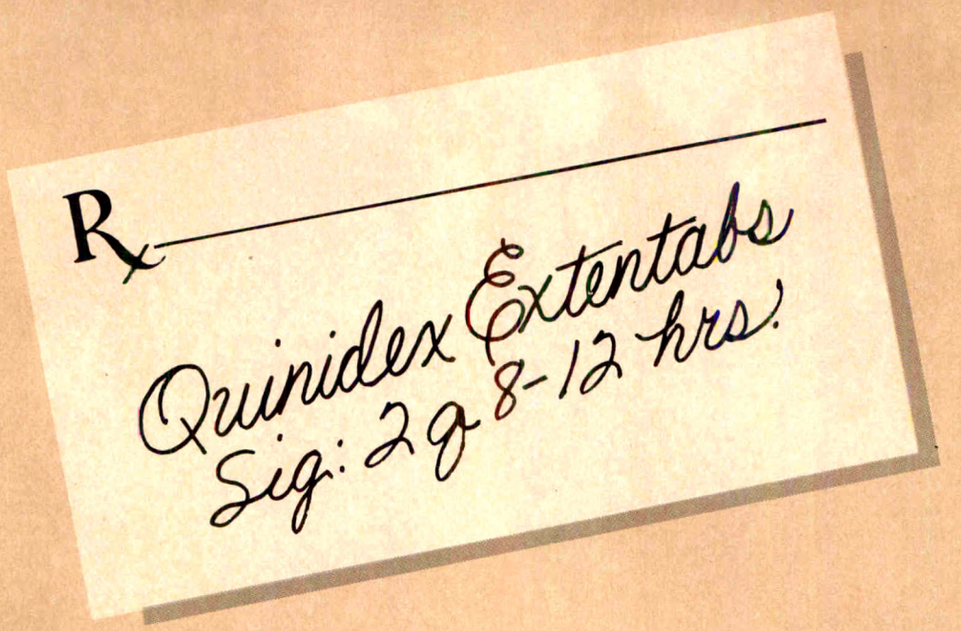
(Quinidine Sulfate, USP)

300 mg in each Extentab

A·H·ROBINS

After the PVC's have been successfully suppressed with quinidine sulfate tablets, you can *maintain* normal sinus rhythm with Quinidex Extentabs. The simple q 8-12 hour dosage is more convenient for the patient than the usual q.i.d. dosage for short-acting tablets. Instead of having to remember to carry his medication with him during the day, he simply leaves the bottle in the medicine cabinet. There's less risk of a missed dose . . . better compliance with your dosage regimen. The unique construction of Quinidex Extentabs provides continuous absorption of quinidine sulfate over an 8-12 hour period. Each of the Extentabs contains 300 mg quinidine sulfate – approximately 23% more quinidine alkaloid than 324 mg quinidine gluconate.

See full prescribing information on following page.



Indications:

Quinidex Extentabs are indicated in the treatment of:

Premature atrial and ventricular contractions.
Paroxysmal atrial tachycardia.
Paroxysmal A-V junctional rhythm.
Atrial flutter.
Paroxysmal atrial fibrillation.
Established atrial fibrillation when therapy is appropriate.
Paroxysmal ventricular tachycardia when not associated with complete heartblock.
Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

The only long-acting form of quinidine sulfate

Quinidex® Extentabs

(Quinidine Sulfate, USP)

A·H·ROBINS

A. H. Robins Company, Richmond, Va. 23220

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.

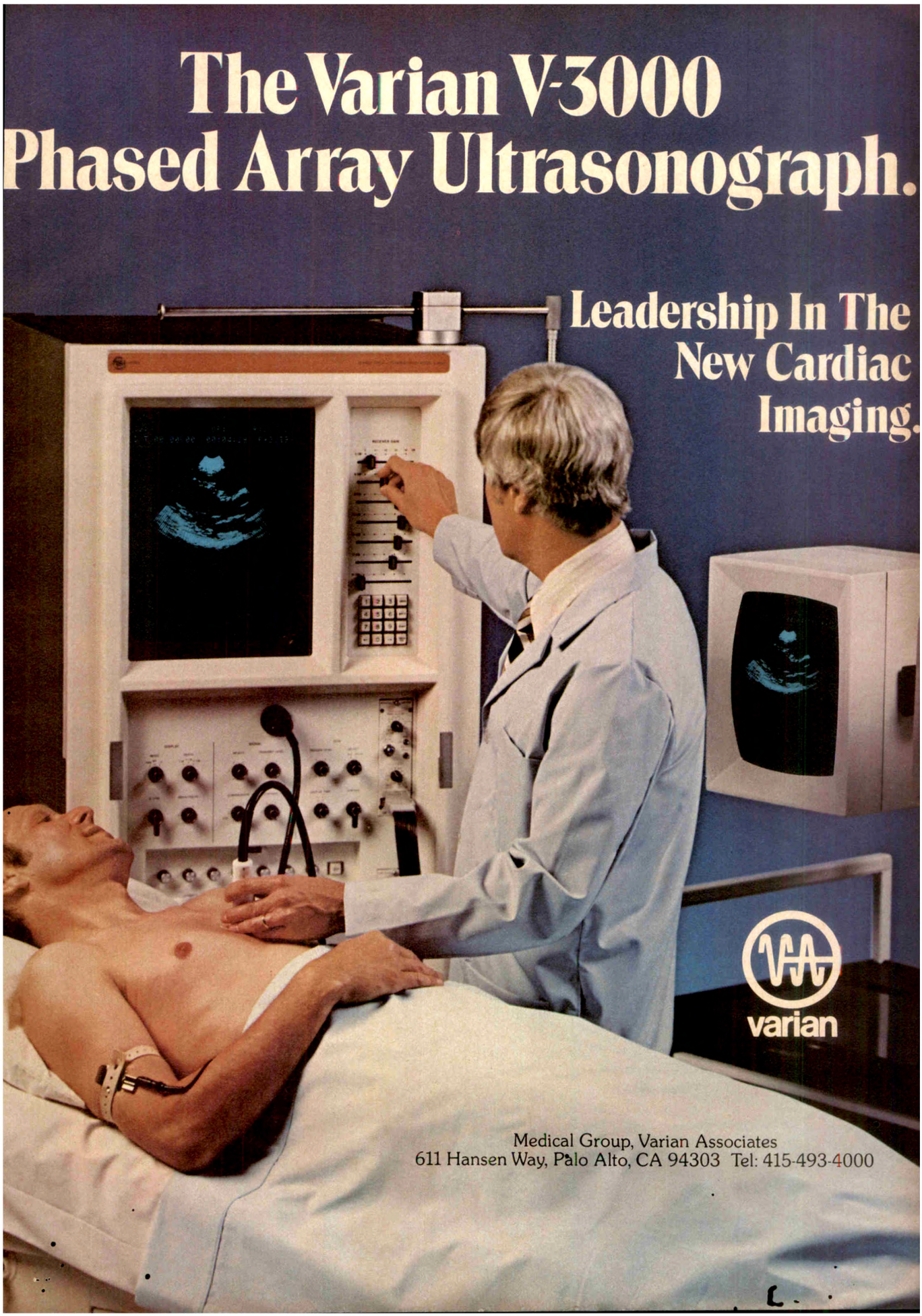
Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 and 250 (NDC 0031-6649).

The Varian V-3000 Phased Array Ultrasonograph.

Leadership In The New Cardiac Imaging.



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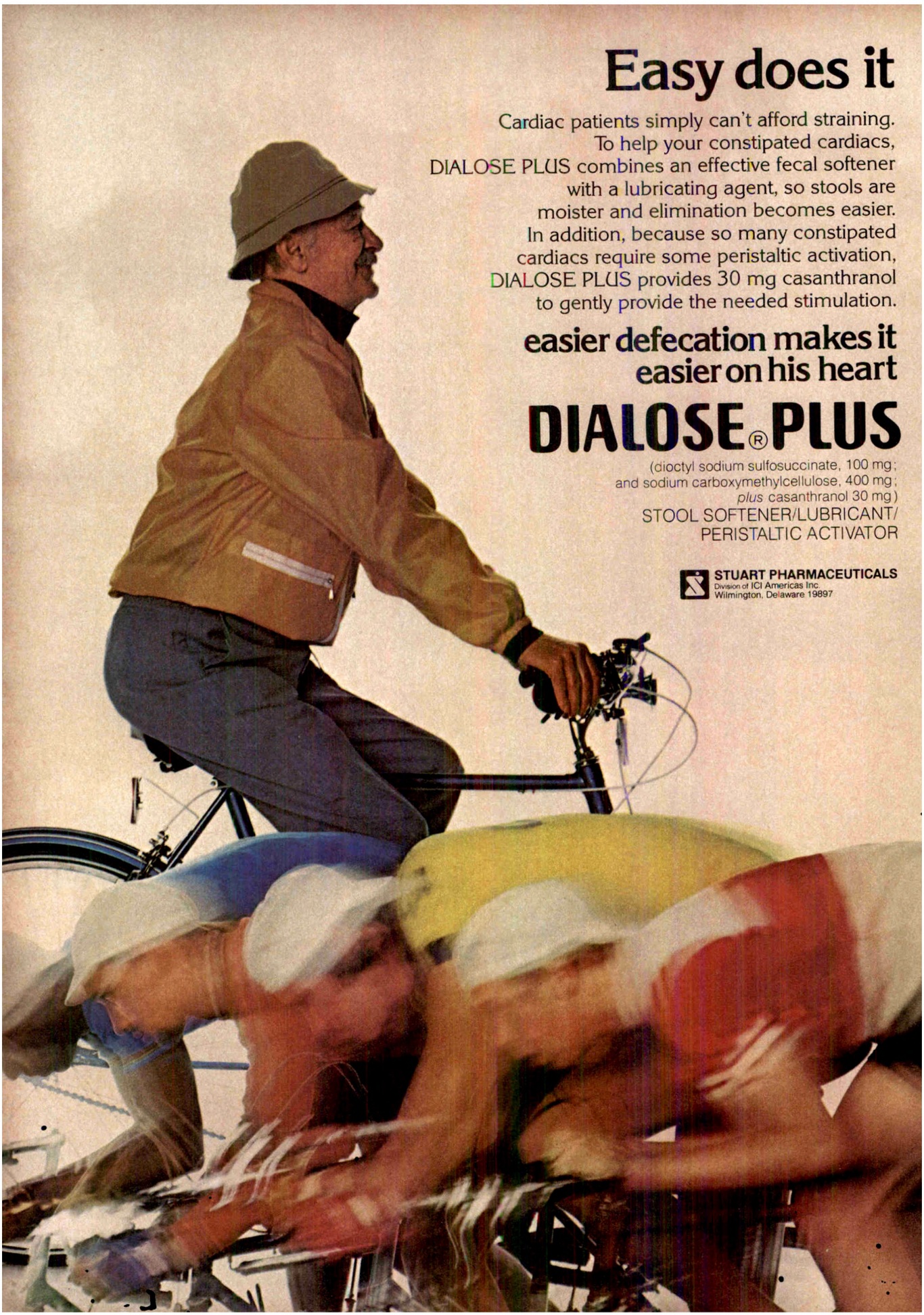
Medical Group, Varian Associates
611 Hansen Way, Palo Alto, CA 94303 Tel: 415-493-4000


Easy does it
Cardiac patients simply can't afford straining.
To help your constipated cardiacs,
DIALOSE PLUS combines an effective fecal softener
with a lubricating agent, so stools are
moister and elimination becomes easier.
In addition, because so many constipated
cardiacs require some peristaltic activation,
DIALOSE PLUS provides 30 mg casanthranol
to gently provide the needed stimulation.
easier defecation makes it
easier on his heart
DIALOSE® PLUS
(dioctyl sodium sulfosuccinate, 100 mg;
and sodium carboxymethylcellulose, 400 mg;
plus casanthranol 30 mg)
STOOL SOFTENER/LUBRICANT/
PERISTALTIC ACTIVATOR
STUART PHARMACEUTICALS
Division of ICI Americas Inc.
Wilmington, Delaware 19897

Variability in Sequential Measures of Left Ventricular Performance Assessed With Radionuclide Angiocardiography

ROBERT C. MARSHALL, MD*
HARVEY J. BERGER, MD
LAWRENCE A. REDUTO, MD
ALEXANDER GOTTSCHALK, MD
BARRY L. ZARET, MD, FACC†

New Haven, Connecticut

The variability of left ventricular ejection fraction, normalized mean ejection rate and regional wall motion was evaluated from first pass quantitative radionuclide angiocardiograms obtained with a computerized multicrystal scintillation camera. Three radionuclide studies separated by an average of 4.3 days were obtained in each of 20 patients. Ejection fraction and ejection rate obtained on the first, second and third studies did not differ significantly. The mean (± standard deviation) variability of sequential ejection fraction measurement was 4.4 ± 3.6 percent, and of sequential ejection rate was 0.56 ± 0.47 sec^{-1}. Variations in measurements were not related to fluctuations in heart rate or blood pressure. Variability in ejection rate was significantly greater in patients with normal function than in those with abnormal function. Regional wall motion analysis was constant in 19 of 20 patients. Thus, sequential quantitative radionuclide angiocardiography allows reproducible serial assessment of left ventricular performance that can be performed with a low level of intrinsic variability.

Newly developed radionuclide techniques allow repeated noninvasive assessment of left ventricular performance. Furthermore, data are frequently obtained from left ventricular time-activity curve analysis. This method is independent of the geometric constraints inherent in conventional measurement of left ventricular pump performance using volume analysis derived from outlines of cavitary silhouettes.[1–8] Because of these favorable characteristics, such techniques appear optimal for evaluating both the natural history of coronary artery disease and the effects of interventions upon left ventricular performance. Before these techniques are applied to sequential studies, the intrinsic variability of radionuclide functional measurements should be defined.

This report describes a study of the day to day variability of left ventricular ejection fraction, normalized mean ejection rate and regional wall motion determined from sequential first pass quantitative radionuclide angiocardiograms in 20 patients. The techniques employed have been validated and standardized in this laboratory.[4–6,9] The data provide a basis for the utilization of this radionuclide method in serial studies of cardiac performance.

Materials and Methods

Patients: Three separate radionuclide angiocardiograms were obtained in each of 20 patients. Individual studies were separated by an average 4.3 days (range 1 to 12 days). All patients were in clinically stable condition in terms of cardiac symptoms and medication during the study period and for at least 1 month prior to study. All had normal sinus rhythm, and none had clinically significant valve regurgitation. Informed consent was obtained from each patient.

All patients were ambulatory men with an average age of 51 years (range 19 to 76). Ten patients had coronary artery disease manifested by previously doc-

From the Cardiology Section, Department of Internal Medicine, and Nuclear Medicine Section, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut. This work was supported in part by National Heart, Lung, and Blood Institute Contract N01HV52988 and Grant ROIHL-21690-01, Bethesda, Maryland. Manuscript received August 9, 1977; revised manuscript received October 3, 1977, accepted October 5, 1977.

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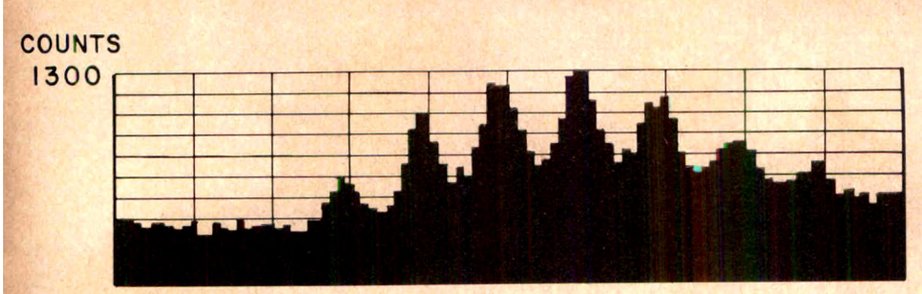

FIGURE 1. Time-activity curve from the left ventricular region of interest. Each peak and valley together constitute one cardiac cycle. Note the peak activity count density of 1,300.

umented transmural myocardial infarction at least 3 months before study. Two patients had clinical evidence of primary myocardial disease. The remaining eight patients had no clinical evidence of cardiac disease and were hospitalized for a variety of noncardiac conditions. One patient with primary myocardial disease and five with coronary artery disease were receiving diuretic agents or digitalis, or both, for treatment of congestive heart failure. No patient was receiving propranolol.

Radionuclide procedures: Radionuclide angiocardiograms were obtained with patients supine in the anterior position using a commercially available computerized multicrystal scintillation camera equipped with a 1.5 inch parallel hole collimator (Baird-Atomic System-77, Bedford, Massachusetts). An 18 gauge polyethylene catheter was placed in a large antecubital vein. A 5 minute rest period was permitted to minimize any sympathetic response associated with the venipuncture. Heart rate and blood pressure were recorded prior to injection. Twenty millicuries (mCi) of technetium-99m pertechnetate dissolved in less than 1 ml of saline solution was injected intravenously and flushed with a 15 ml bolus dose of normal saline solution. This is a radionuclide dose comparable with that routinely used for clinical brain scanning in many institutions. The maximal whole body radiation burden of a single study is 0.40 rads. First pass radionuclide angiocardiographic data were accumulated in frame mode at 0.05 second intervals during the 25 seconds of initial radionuclide transit through the central circulation. Data were stored on magnetic disc. Data were processed immediately after each study by one investigator (R.C.M.).

Data processing: Left ventricular ejection fraction, normalized mean ejection rate and regional wall motion were determined according to previously described techniques.[4-6] Briefly, the left ventricular region of interest was identified from an oscilloscopic serial display of the entire radionuclide angiocardiogram, with each image representing the sum of 20 individual 0.05 second frames. A preliminary high frequency time-activity curve was generated from this region of interest (Fig. 1). End-diastolic frames, identified as high count peaks in the left ventricular time-activity curve, were used as starting points to sum together counts at corresponding 0.05 second intervals over three to six (average four) cardiac cycles. A series of sequential background frames were chosen directly from the left ventricular time-activity curve at a time just prior to the first discernible left ventricular beat at the beginning of the left ventricular phase. The summed background was subtracted from the summed cardiac cycle forming a high count rate, background-corrected "representative" cardiac cycle, which is the equivalent of a relative ventricular volume curve (Fig. 2).

Left ventricular ejection fraction (EF) was calculated directly from the representative cardiac cycle according to the formula:

$$EF = \frac{ED\ c - ES\ c}{ED\ c} \times 100$$

where c = counts; ED = end-diastolic and ES = end-systolic. Normalized mean left ventricular ejection rate (dc/dt/c average) was determined from the same representative cycle. The ejection phase was fitted to a weighted least squares straight line. The slope of this line (dc/dt) was then normalized to the average counts (c average) over the ejection phase. Regional wall motion was evaluated from composite images formed by superimposing a computer-generated end-diastolic contour upon the end-systolic image (Fig. 3). Regional wall motion was interpreted as either normal or abnormal (severely hypokinetic or akinetic). For analysis, single anterior position wall motion images were divided into anterolateral, apical and inferior segments. In these single position studies, the septal and posterolateral walls were not evaluated.

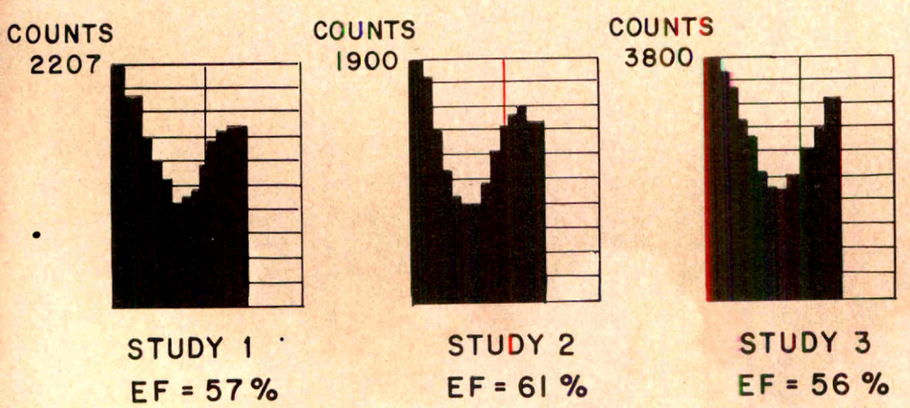

FIGURE 2. Case 12. Representative cycles (relative volume curves) formed by summing activity from individual cardiac cycles. Ejection fraction (EF) is calculated directly from these curves. Data from three sequential studies are shown.

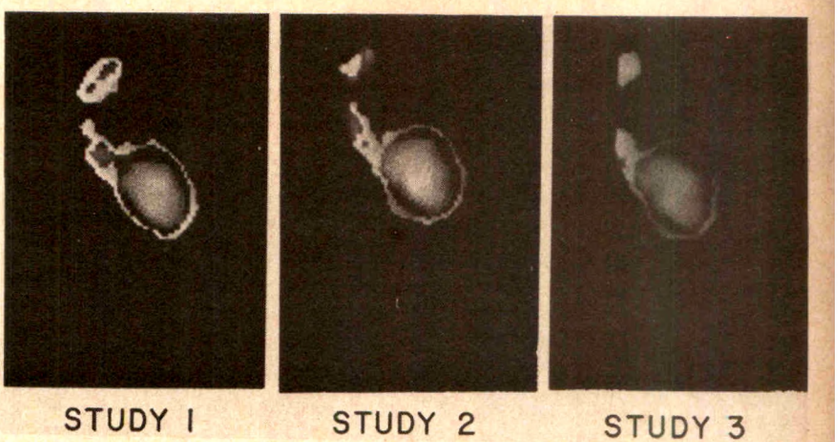

FIGURE 3. Case 19. Sequential regional wall motion studies obtained in the anterior position. In the composite images, the outer ring represents the computer-generated end-diastolic contour. The image within this ring represents end-systole. Note the comparability of the anteroapical regional wall motion abnormality in the three studies.

Ejection fraction determined in this manner correlates well with contrast angiographic measurements and is a reproducible value when repeated within 30 minutes.[4,6] Normalized mean ejection rate correlates well with ejection fraction but also appears to provide enhanced sensitivity for detection of pharmacologic changes in inotropic state.[5,6,9] In addition, regional wall motion assessed with this radionuclide technique agrees closely with analysis obtained from left ventricular contrast angiography.[4,6]

Statistical methods: To determine the variability of the technique, the absolute differences in ejection fraction and normalized mean ejection rate between study 1 and study 2, study 1 and study 3, and study 2 and study 3 were determined for each patient. The mean ± standard deviation of these values represents the variability of each radionuclide index of ventricular performance.

Data are expressed as the mean ± standard deviation (SD). Linear regression equations and correlation coefficients were obtained in a standard manner. Comparison of sequential studies were made by paired t test.

Results

Left ventricular ejection fraction and ejection rate: Data obtained in the three sequential studies are shown in Table I and illustrated in Figures 4 to 7. Left ventricular ejection fraction and ejection rate obtained on the first, second and third studies did not differ significantly ($P > 0.05$), and individual measurements correlated well with each other (Fig. 6). Left ventricular ejection fraction averaged 52 ± 21 percent for study 1, 50 ± 20 percent for study 2 and 51 ± 21 percent for study 3. However, there was variation in measurements in individual patients. The mean variability of sequential ejection fraction measurement was 4.4 ± 3.6

TABLE I

Results of Three Sequential Radionuclide Measures of Left Ventricular Performance, Mean Blood Pressure and Heart Rate in 20 Patients

Case no.	Ejection Fraction (%)			Normalized Mean Ejection Rate (sec^{-1})			Mean Blood Pressure (mm Hg)			Heart Rate (beats/min)		
	1	2	3	1	2	3	1	2	3	1	2	3
1	66	64	58	2.91	3.29	2.78	88	108	88	70	96	70
2	69	62	66	4.54	3.48	3.62	76	87	84	52	58	52
3	32	32	27	1.53	1.40	1.28	95	105	110	78	78	86
4	24	30	27	1.08	1.01	0.80	93	96	100	90	80	82
5	71	63	75	4.29	3.33	3.75	103	106	104	80	84	76
6	22	30	25	0.83	1.21	1.05	122	97	103	82	86	88
7	84	82	81	5.39	5.72	4.08	90	90	83	64	66	70
8	47	57	53	2.48	2.85	2.67	113	113	105	74	84	80
9	72	66	58	4.74	3.50	2.65	87	84	95	78	74	76
10	81	82	84	4.51	4.93	5.40	103	111	104	82	76	76
11	66	67	66	4.02	4.40	3.22	104	97	101	92	82	86
12	57	61	56	2.67	3.82	2.50	77	80	70	72	76	66
13	42	29	31	1.39	1.06	1.72	101	115	102	76	80	78
14	36	34	35	2.19	2.27	1.79	108	124	124	92	96	94
15	13	13	20	0.33	0.33	0.69	83	72	72	78	70	82
16	53	47	48	2.60	2.31	2.06	95	92	85	76	70	80
17	67	52	60	4.37	2.55	2.88	90	100	85	96	86	76
18	34	29	35	1.29	1.07	1.70	88	78	77	84	88	90
19	30	29	33	0.85	1.09	1.21	77	78	73	84	68	72
20	67	66	74	4.21	4.11	4.99	93	106	98	84	84	96

percent. Five patients had a greater than 10 percent change in left ventricular ejection fraction between two evaluations. The greatest absolute change in ejection fraction between any two studies in the same patient was 15 percent. No patient had any change in clinical status. There was no significant interstudy difference in blood pressure or heart rate distinguishing studies with a greater than 10 percent change in ejection fraction from those with smaller changes. Heart rate and mean blood pressure differed between studies by 6 ± 4 beats/min and 6 ± 4 mm Hg, respectively, in cases with interstudy ejection fraction differences of more than 10 percent, and 8 ± 4 beats/min and 7 ± 5 mm Hg, respectively, for cases with interstudy ejection fraction differences of less than 10 percent. Furthermore, the

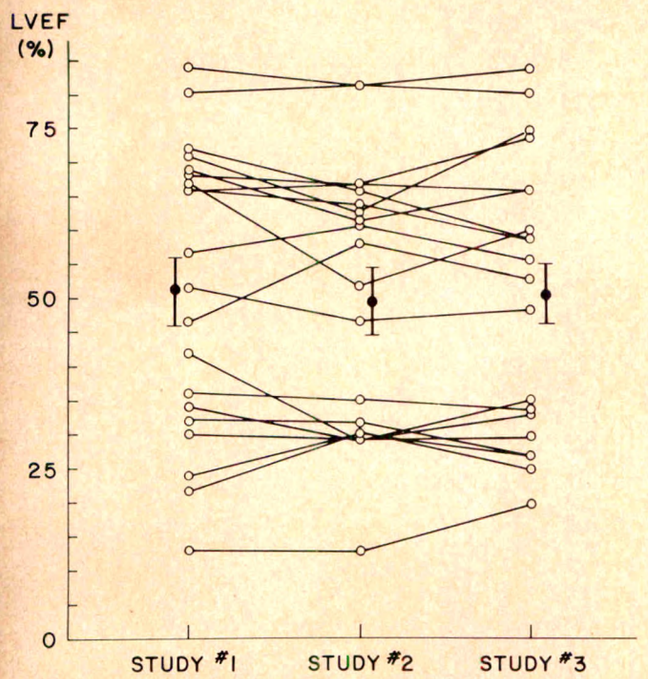

FIGURE 4. Sequential left ventricular ejection fraction (LVEF) measurements in 20 patients. The **open circles** connected by lines indicate data for each patient. **Closed circles and bars,** respectively, indicate mean values and standard errors for the entire group.

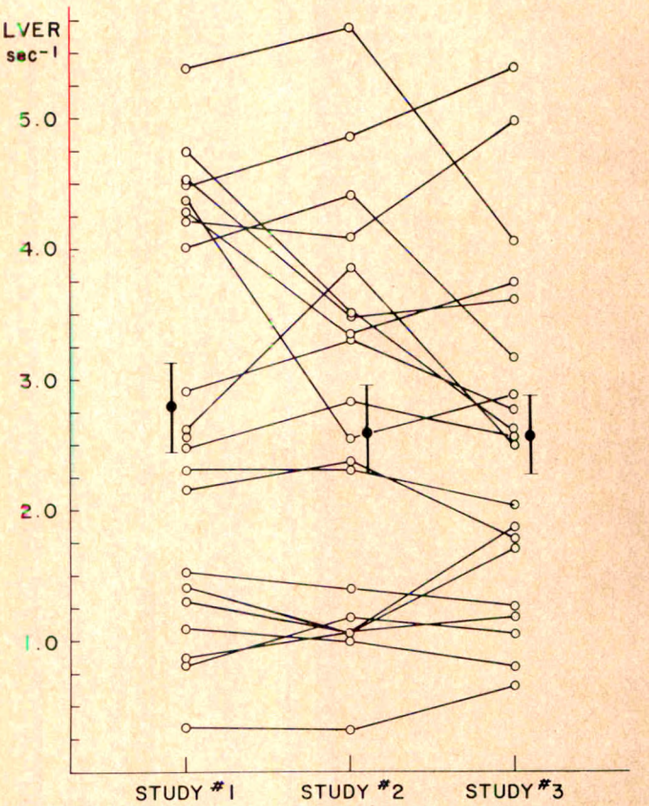

FIGURE 5. Sequential left ventricular ejection rate (LVER) measurements in 20 patients. Format as in Figure 4.

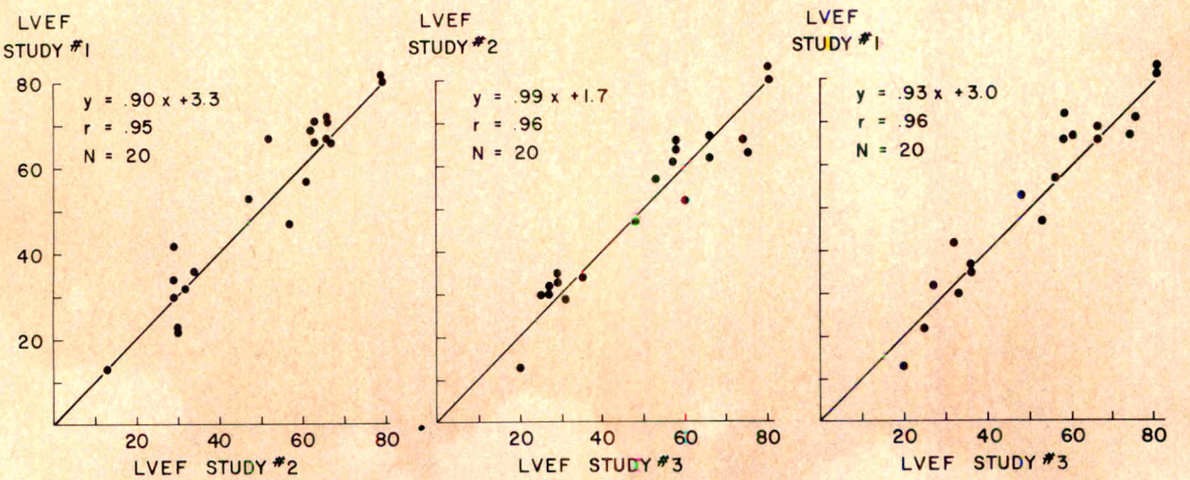

FIGURE 6. Interstudy correlations for left ventricular ejection fraction (LVEF) based on three sequential evaluations. The relation between data obtained in study 1 and study 2 is shown in the **left panel,** between study 2 and study 3 in the **middle panel** and between study 1 and study 3 in the **right panel.** In each instance the regression equation and correlation coefficient are given, and the line of identity is drawn. Note the excellent correlations.

interstudy variation in ejection fraction in patients with normal left ventricular performance (ejection fraction greater than 50 percent) and those with abnormal performance did not differ significantly. The mean difference in patients with normal performance was 4.8 ± 3.9 percent, and the mean difference in patients with abnormal performance was 4.2 ± 3.1 percent ($P > 0.05$).

Normalized mean left ventricular ejection rate averaged 2.81 ± 1.58 sec^{-1} on day 1, 2.68 ± 1.50 on day 2, and 2.54 ± 1.30 on day 3 ($P > 0.05$). The mean variability of sequential measurement of normalized mean ejection rate was 0.56 ± 0.47 sec^{-1}. The largest absolute difference in ejection rate between any two studies was 2.09 sec^{-1}. Interstudy variation in normalized mean ejection rate was not related to changes in heart rate or blood pressure. However, in contrast to ejection fraction findings, there was significantly greater interstudy variation in ejection rate in normal subjects (ejection rate more than 2.50 sec^{-1}) than in abnormal subjects. The mean difference in normal subjects was 0.83 ± 0.53 sec^{-1}, and in abnormal subjects was 0.29 ± 0.17 sec^{-1} ($P < 0.001$).

Regional wall motion: In 13 patients, reproducibly normal regional wall motion was present in each of the three studies. Seven patients had demonstrable regional wall motion abnormalities. In all but one patient, the wall motion abnormality was of comparable magnitude and location in all studies (Fig. 3). One patient (Case 13) demonstrated anteroapical akinesia only on the second and third studies. No change in this patient's clinical status or electrocardiogram occurred over the period of study.

Blood pressure and heart rate: For the entire group, values for mean blood pressure during the first, second and third studies were 94 ± 12, 96 ± 14, and 93 ± 14 mm Hg ($P > 0.05$ for each comparison). Mean values for heart rate were 79 ± 10, 79 ± 10, and 79 ± 10 beats/min for studies 1, 2 and 3, respectively. There were no statistically significant differences among any of these values.

Technical factors: Analysis of technical factors involved in data processing did not reveal significant interstudy variation. Background subtraction, determined as percent of the uncorrected peak end-diastolic activity, averaged 35 ± 6 percent for study 1, 34 ± 8 percent for study 2 and 36 ± 7 percent for study 3 ($P > 0.05$). The number of crystals selected in the left ventricular area of interest averaged 25 ± 9 for study 1, 26 ± 8 for study 2 and 26 ± 9 for study 3 ($P > 0.05$). Peak end-diastolic counts averaged 3,300 ± 2,000 and did not vary significantly among studies.

Discussion

The intrinsic variability of sequential radionuclide measurement of left ventricular ejection fraction, normalized mean ejection rate and regional wall motion was acceptably small in this study. At the radioactivity count rates encountered, the statistical uncertainty of measurements averaged approximately 2 percent. There were no significant differences in left ventricular ejection fraction and ejection rate measured in each of three sequential evaluations. Regional wall motion analysis was likewise a relatively stable measurement over the course of three studies. Only 1 of 20 patients demonstrated any significant change in analysis of regional wall motion.

Significance of interstudy variation in measurements: Despite the overall agreement between studies for the entire group, five patients occasionally demonstrated interstudy variation in measurements of left ventricular performance. This variation was not attributable to changes in heart rate or blood pressure, which are physiologic factors previously shown to affect measurement of ejection fraction.[10,11] Likewise, technical factors were not related to interstudy variation. The frequency of this degree of variation may decrease as a larger number of patients are studied. Thus, al-

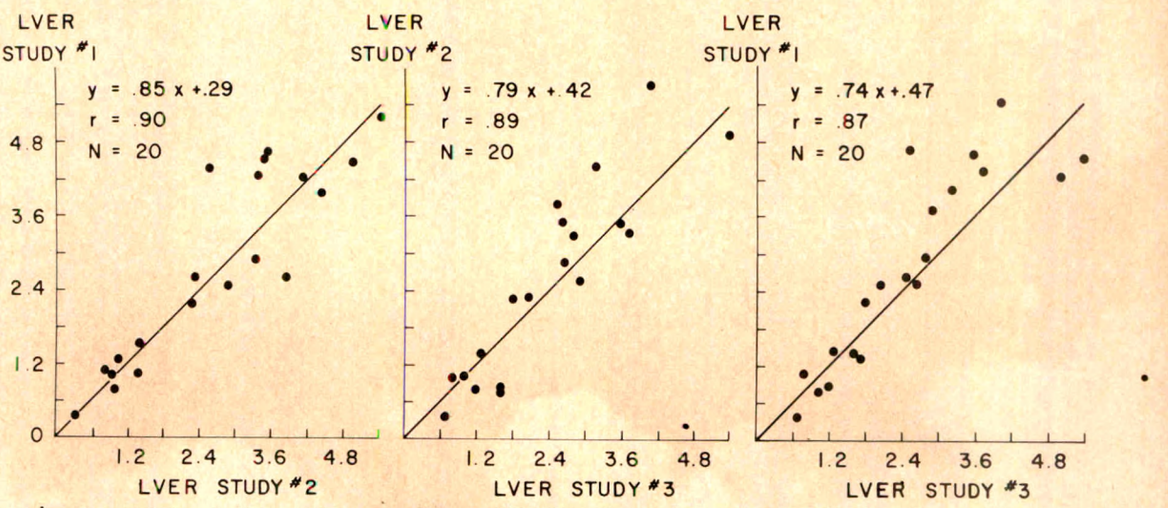

FIGURE 7. Interstudy correlations for left ventricular ejection rate (LVER) based on three sequential evaluations. Format as in Figure 6. Note the greater scatter around the line of identity in patients with a normal ejection rate.

though serial noninvasive radionuclide evaluation of left ventricular performance appears to be suited for long-term follow-up of patient groups, care should be taken in interpreting the relevance of a single interstudy difference in any one patient. In view of the data presented on intrinsic variability of ejection fraction measurement, an interstudy difference of at least 5 percent would be required for the change to be considered meaningful. Repeated sequential evaluation is needed to establish a more definite trend. Furthermore, in patients with normal baseline left ventricular performance, ejection rate appears to be a relatively labile measurement. The same degree of variation was not noted in patients with depressed baseline performance. This lability of ejection rate in normal subjects may represent the sensitivity of this measurement to more subtle changes in pump performance in patients with good ventricular reserve, induced perhaps by normal variations in sympathetic activity.

Comparison with results of left ventricular angiography: The results of this radionuclide study can be compared with data from two previous reports involving contrast left ventricular angiography. McAnulty et al.[12] evaluated left ventricular function sequentially by performing cardiac catheterization and angiography on 2 successive days. No significant interstudy change was noted in the mean values of any index of left ventricular performance measured. However, marked individual variability was encountered in all measured indexes with the exception of regional wall motion analysis. Our radionuclide results are similar to McAnulty's. Absolute change in ejection fraction over two studies averaged (± standard deviation) 4 ± 10 percent in that study compared with 4.4 ± 3.6 percent in our study. Cohn et al.[13] also evaluated the reproducibility of contrast angiographic left ventricular ejection fraction measured in two sequential studies performed either in the course of a single cardiac catheterization or within 2 to 4 days of each other. Ejection fraction obtained from studies separated by 30 minutes varied by 4 percent, while measurements obtained from studies separated by 90 minutes varied by 4 to 8 percent. However, in patients studied at intervals of 2 to 4 days, ejection fraction varied by 13 percent. Furthermore, ejection fraction obtained in the second study was significantly higher than in the first.

Clinical implications: This study demonstrates that sequential radionuclide angiocardiography allows reproducible serial assessment of left ventricular performance that can be performed with a low intrinsic variability. This variability might be expected to be even less in the near future when higher count rate data are acquired at frame rates faster than the current 20 frames/second.[14] Unlike cardiac catheterization and contrast angiography, these studies are not accompanied by additional physiologic changes resulting from varying amounts of blood loss, fluid replacement and hypertonic contrast-induced diuresis. Because of the noninvasive and physiologic nature of this technique, it appears to ideally suited for study of the natural history of heart disease and the effects of medical and surgical interventions upon left ventricular performance.

Acknowledgment

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Measurement of Atrial Septal Defect During Cardiac Catheterization

Experimental and Clinical Results

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The size of experimental and clinical secundum atrial septal defects may be accurately measured during cardiac catheterization. The position of the defects in the septum and their distance from the aortic and mitral valves may also be ascertained. A balloon catheter inflated with radiopaque dye is used for the measurement. The volume of dye in the balloon has been correlated with its maximal diameter. Thus, a no. 8-10 French catheter filled with 10 ml of diatrizoate (50 percent) has a diameter of approximately 25 mm and a no. 8-22 French catheter filled with 40 ml of diatrizoate a diameter of approximately 43 mm. Persistent arrhythmias or other adverse effects of the procedure were not observed. There was a high correlation between balloon-measured atrial septal defects and those measured at necropsy in the animals or at operation in the patients. These measurements aid in determining whether an ostium secundum defect is of proper size and location to be closed transvenously and may also prove valuable in physiologic studies of atrial septal defects or other cardiac anomalies.

Several modes of management are possible for the uncomplicated secundum atrial septal defect. Spontaneous closure has been reported clinically[1,2] and in the experimental animal.[3] Nonoperative closure of the secundum atrial septal defect has been carried out in 11 patients.[4–6]

We have developed a practical technique for measuring the size and estimating the configuration and location of an atrial septal defect during the course of experiments relating to noninvasive closure. In this paper we describe our technique for transvenous measurement of the size of an atrial septal defect during cardiac catheterization. With further scientific data, this technique may assist in determining criteria for surgical closure and provide additional information regarding the natural history of the size of small secundum atrial septal defects.

Technique of Measurement

Experimental Method

The atrial septal defects of 11 dogs were measured after they had been created 1 to 7 days earlier with a punch biopsy technique.[7] The initial five animals were killed within 24 hours and the defects measured under direct vision to determine the relation between the size of punch instrument chosen and the defect it provided. Balloon measurement of the defect was not carried out in this group. The remaining six dogs were anesthetized with sodium pentobarbital to a stable hemodynamic state with spontaneous respiration and without significant cardiac arrhythmias. Sizing was carried out a minimum of three times. After confirmation of the atrial septal defect, a balloon catheter (Fogarty catheter no. 2179904, Edwards Laboratory, Santa Ana, California) was introduced through the right femoral vein. The guide wire of the catheter was gently curved to allow the distal end to be manipulated across the atrial septal defect into the body of the left atrium, and hence toward the left atrial appendage in order to confirm the bal-

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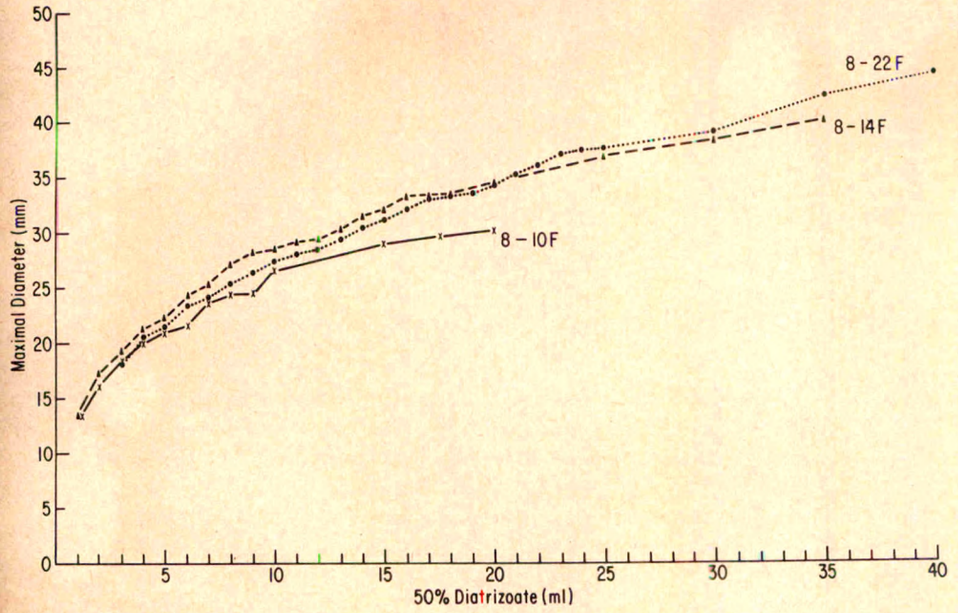

FIGURE 1. Nomogram showing the relation between maximal balloon diameter and volume of dye within the balloon. Three different catheter sizes (8-10, 8-14 and 8-22 French) are demonstrated. This nomogram represents experimental testing of 30 catheters. The standard deviation was ±1.5 mm for all three catheter sizes for any given volume of contrast material.

loon position with fluoroscopy. The catheters, no. 8-10, 8-14 and 8-22 French, consisted of a single lumen with a deflated balloon near the distal tip. A preliminary general estimate of the size of the atrial septal defect could be made with use of left atrial cineangiocardiography and the size of the punch used to create the defect. From previous experiments and as experience was gained, we found that a no. 8-10 French catheter could be used with an atrial septal defect with an expected diameter of up to 30 mm. This catheter is introduced through a no. 9 arterial sheath (USCI, Division of C. R. Bard, Inc, Glen Falls, New York). For a larger defect (for example, one with a diameter of 25 to 45 mm), a no. 8-14 French catheter was appropriate, and for one greater than 40 mm in diameter, a no. 8-22 French catheter was used. A cutdown procedure is required for introduction of these catheters.

After the balloon was advanced into the left atrium, it was inflated with sodium diatrizoate (50 percent Hypaque®) to a size anticipated to be larger than the atrial septal defect, as indicated from the estimate based on punch size and the cineangiocardiogram. A dye solution more concentrated than 50 percent is difficult to remove from the balloon, and the size of the balloon varies with different concentrations of dye. The usual initial capacity was 10 ml of dye in the 8-10 French catheter. Care was taken to remove all air from the balloon before inflating it in the heart. The inflated balloon catheter was then withdrawn from left to right until it encountered the resistance of the septum. The balloon was deflated in 0.5 ml aliquots until it passed snugly through the atrial septal defect into the right atrium. If the balloon proved to be too small with the initial 10 ml of contrast material, a larger volume of contrast material or a larger catheter, or both, was used and the same steps were taken. From the volume of dye that remained in the balloon, the maximal diameter of the atrial septal defect was calculated with use of a nomogram (Fig. 1). Balloon di-

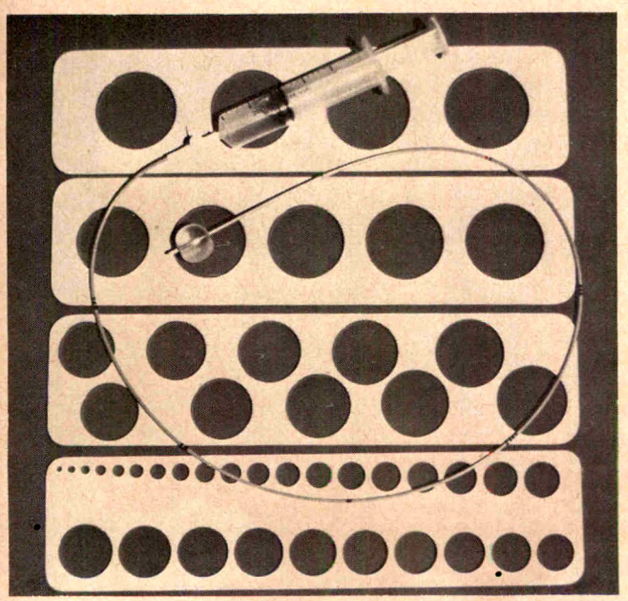

FIGURE 2. Calibrated aluminum plates with circular holes starting at 3 mm and graduated every 1 mm to 50 mm. An 8-10 French Fogarty catheter with an inflated balloon is also shown.

TABLE I

Correlation of Amount of Dye and Balloon Rupture* (30 Catheters)

Size of Catheter	No Balloon Rupture		Balloon Rupture (average)
	Ochsner Foundation Laboratory	Edwards Laboratory	
8-10F	≤22	≤25	30
8-14F	≤35	≤46	70
8-22F	≤100	≤200	243

* Data presented as milliliters of 50 percent Hypaque.

TABLE II

Correlation of Size of Experimental Atrial Septal Defect, Balloon Measurement and Postmortem Findings

Dog no.	Punch Trocar Size (mm)	Postmortem Ruler Examination (mm)	Size of Defect: Transvenous Balloon Measurement (mm) 8-10	8-14	8-22	Postmortem Balloon Measurement (mm) 8-10	8-14	8-22
1	15	12	...	...	...	...	...	...
2	15	15	...	...	...	...	...	...
3	15	14	...	...	...	...	...	...
4	15	17	...	...	...	...	...	...
5	15	18	...	...	...	...	...	...
6	10	13	16	16	16	16	16	16
7	10	12	14	12	13	14	12	13
8*	15	16	20	20	18	20	20	18
9†	15	20	23	23	21	22	22	23
10	15	18	19	20	19	19	20	19
11	15	18	19	19	19	19	19	20

* Maximal discrepancy postmortem between balloon and ruler measurement = 4 mm.
† Maximal discrepancy postmortem between punch and ruler measurement = 5 mm.
Dogs 1 to 5 were killed within 24 hours and the atrial septal defects were measured under direct vision. Balloon sizing was not performed in this group.

ameters were determined using calipers and a series of calibrated circular holes graduated every millimeter of diameter from 3 to 50 mm (Fig. 2).

The nomogram was derived by comparing the maximal balloon diameter and volume of dye within the balloons in 30 catheters. Three catheter sizes were used (8-10, 8-14 and 8-22 French). In catheters of each size serial increments of dye in milliliters were correlated with the maximal diameter in millimeters, using 10 catheters of each size to determine the standard deviation. The amount of dye that could be safely used to inflate the balloon without rupture and the average amount of dye necessary to cause balloon rupture are shown in Table I.

Clinical Method

Twenty-five patients thought to be candidates for umbrella closure of an atrial septal defect had the defect sized with the balloon technique at cardiac catheterization. The patients were carefully instructed on the experimental nature of the project and all gave informed consent. The study was cleared by the Clinical Investigations Committee of the Alton Ochsner Medical Foundation. The patients were sedated with meperidine hydrochloride (Demerol®), 1 mg/kg body weight to a maximal dose of 50 mg, and promethazine hydrochloride (Phenergan®), 0.25 mg/kg. After routine cardiac catheterization, the pulmonary to systemic flow ratio was determined with the Fick method and left cineangiocardiography was performed. The size of the atrial septal defect was estimated from the pulmonary to systemic flow ratio (Qp:Qs ratio) and the cineangiocardiographic studies.

The atrial septal defects were measured with a size 8-10 French catheter because a catheter of this size can be passed through a no. 9 arterial sheath percutaneously using the femoral vein. The larger catheters require a cutdown procedure. We now consider it safe to use more dye (up to 20 ml) than was used early in the study because no balloon rupture occurred with less than 22 ml of contrast material. By referring to the nomogram correlating the amount of contrast material with the diameter of the catheter (Fig. 1), we were able to make an accurate estimate of the size of the atrial septal defect.

The balloon was then repositioned in the left atrium and inflated to a diameter slightly greater than that of the atrial septal defect as determined from the previous measurement. The balloon was then fitted snugly in the defect while fluoroscopy was performed in anteroposterior, left antero-oblique and right antero-oblique positions. The position of the atrial septal defect on the atrial septum and its relation to the aortic and mitral valves were further documented with a simultaneous left ventricular cineangiogram while the balloon was wedged in the defect. Patients not considered candidates for umbrella closure of the atrial septal defect had routine defect closure with the standard open heart surgery technique. The defect was palpated before cardiopulmonary bypass and during cardiopulmonary bypass with anoxic arrest; it was then inspected and carefully measured after a right atriotomy was performed.

Five patients had umbrella closure of their defect[5]; in these cases it was not possible to confirm the size of the atrial septal defect measured with the balloon catheter technique.

Results

Experimental Results

In the dog studies, the punch biopsy technique created a defect comparable in size with the size of trocar used (difference 0 to 5 mm, mean 2.4). Defects of various sizes could be produced with the use of different trocars.[7] The diameters of the defects as measured with the dye-inflated balloon technique and at necropsy correlated within 4 mm (Table II). The 8-22 French catheter was found best for sizing a large atrial septal defect because it reached a diameter of approximately 43 mm when inflated with 40 ml of contrast medium (Fig. 1). Use of the large catheter minimized the risk of balloon rupture and possible fragmentation and embolization.

Clinical Results

No significant complications or persistent arrhythmias were associated with the sizing technique in the 25 patients. Temporary balloon occlusion of the atrial septal defect did not alter the vital signs and was not associated with pain. The shunt calculations ranged from 1.6:1 to greater than 4:1 by

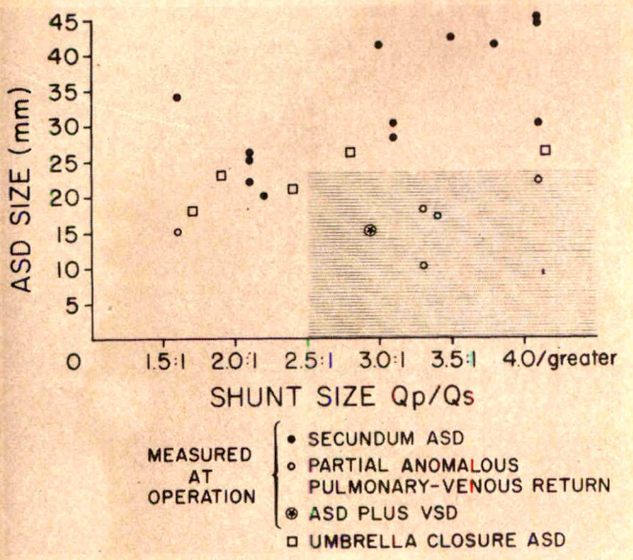

FIGURE 3. Scattergram relating the size of the atrial septal defect (ASD) to the degree of left to right shunting (Qp:Qs ratio). Atrial septal defect measurements were made at operation except in five patients who underwent umbrella closure of their defect. Measurements of atrial septal defects at catheterization differed only up to 5 mm from those at operation (mean deviation ±2.1 mm). Larger shunt sizes with smaller atrial septal defects **(shaded area)** should alert one to the possibility of anomalous pulmonary venous return. VSD = ventricular septal defect.

oxygen study and were related to the size of the defect as measured with the balloon technique and confirmed during open heart surgery (Fig. 3). Because atrial septal defects with a diameter of more than 30 mm were not considered for umbrella technique, larger balloons to determine the exact size of the defect were not used. The size of the defect measured at catheterization differed up to 5 mm from that measured at operation with a mean deviation of ±2.1 mm (Table III).

From the left ventricular cineangiograms obtained in the right anterior oblique view with the balloon-filled catheter occluding the atrial septal defect, we could determine whether the defect was superior, inferior or central in the septum (Fig. 4). The levogram phase of an anteroposterior cineangiogram (Fig. 5) revealed the relation of the mid portion of the atrial septum to the aortic valve.

Three patients with a central septal defect as determined with balloon occlusion and simultaneous cineangiography underwent attempted closure with an umbrella that was too small. The left atrial umbrella in each instance was pulled across the septum into the right atrium and was thereafter brought back to the capsule. Instead of inserting a larger umbrella, routine open heart closures were performed.

The five patients who underwent umbrella closure of the atrial septal defect we believe had adequate assessment of the size and position of their atrial septal defect and to date have had an uncomplicated course after closure (Table III).[5]

Discussion

Atrial septal defects, 10 to 20 mm in size, of the central secundum variety in the nonfilled, fibrillating or ischemic heart seem more oval than round at operation; however, in the beating functioning heart assessment with digital palpation and balloon sizing indicates that these defects are actually round. The experimental defects, although created round in the dogs, appeared at necropsy to be oval. When a balloon was placed in the atrial septal defect to resize it at necropsy, the defect assumed a round configuration without being distorted by the balloon itself.

Potential complications of technique: With the balloon measurement technique one can accidentally enlarge the atrial septal defect in the manner that occurs purposely with the Rashkind septostomy. However, by

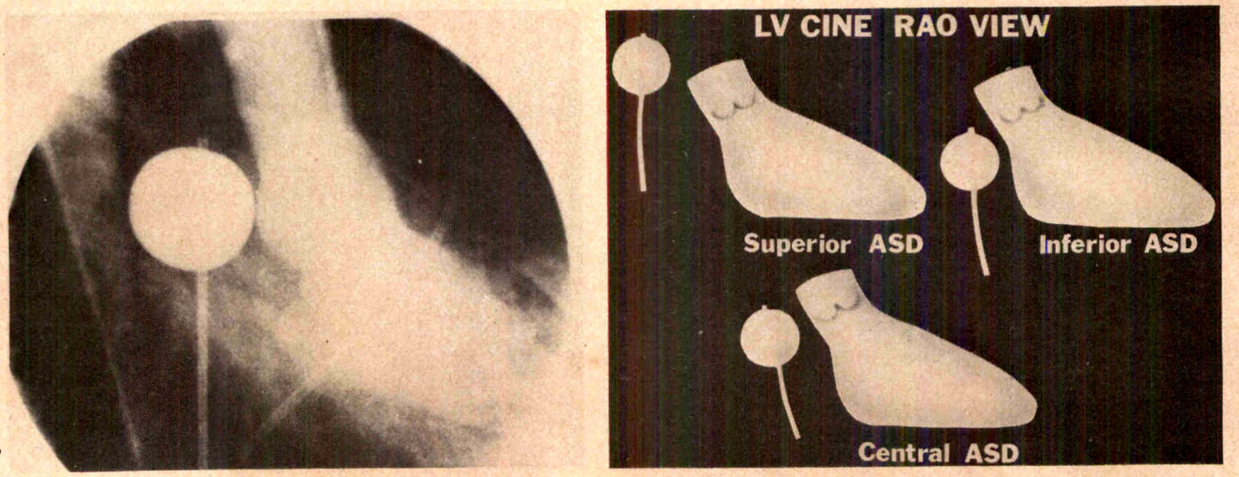

FIGURE 4. Determination of location of atrial septal defect (ASD). **Left,** frame from left ventricular cineangiogram (LV CINE) in right anterior oblique (RAO) view with the balloon wedged in the defect. The filled balloon catheter is at the level of the aortic valve; in our experience, this indicates a centrally located defect (secundum). Note the distance between the inferior balloon rim and the mitral valve anulus. **Right,** diagram of the sizing balloon when wedged in the atrial septal defect as related to the aortic valve during left ventricular cineangiography. The balloon is superior to the aortic valve in a superior defect, adjacent to the valve in a central defect and inferior to the valve in an inferior defect.

TABLE III

Balloon Measurement of Atrial Septal Defects in 25 Patients

Case no.	Age (yr) & Sex	Shunt Size Qp:Qs	ASD Size (mm) Balloon	ASD Size (mm) Operative	Comment
1	17F	2.8-1	26	. . .	35 mm umbrella
2	17M	1.7-1	18	. . .	25 mm umbrella
3	44M	2.4-1	21	. . .	30 mm umbrella
4	24F	1.9-1	23	. . .	30 mm umbrella
5	75M	>4.0-1	20, 7, 5	. . .	30 mm umbrella
6	32M	3.1-1	26	24	. . .
7	9M	4.1-1	>30	45	Inferior secundum ASD
8	34F	3.4-1	17	17	PAPVR
9	10/12F	3.5-1	>30	42	Common atrium
10	11F	2.1-1	21	22	Sinus venosus
11	5M	2.9-1	13	15	Associated VSD
12	54F	2.1-1	24	25	. . .
13	53F	4.1-1	>30	44	No posterior ASD rim
14	29F	3.0-1	29	30	Low ASD
15	23F	2.1-1	26	26	Umbrella too small
16	5F	1.6-1	15	15	PAPVR
17	5M	2.2-1	23	20	. . .
18	34M	1.6-1	38	34	Coronary artery disease
19	43M	3.1-1	26	28	. . .
20	5F	3.8-1	>30	>40	Small inferior rim
21	48F	4.1-1	31	30	. . .
22	14M	3.3-1	15	10, 4, 3	Sinus venosus
23	9F	3.3-1	16	18	PAPVR
24	15M	>4.0-1	20	21, 5	PAPVR
25	5M	3.0-1	40	41	. . .

ASD = atrial septal defect; PAPVR = partial anomalous pulmonary venous return; Qp:Qs = pulmonary to systemic flow ratio; VSD = ventricular septal defect.

taking minimal care and gently advancing the balloon across the defect, we avoided this complication, and we found no evidence of damage or tear in patients referred for operation after balloon measurement. A potential complication is impairment of venous return by an inappropriately placed balloon (for example, in the inferior vena cava or tricuspid valve) if there is a delay in deflation. This has not occurred in our experience and should easily be avoided. With large volumes of contrast solution, the balloon tends to move toward the mitral valve; however, this movement can be prevented or minimized with gentle traction on the catheter. In one patient the balloon floated into the pulmonary artery in the manner of a Swan-Ganz catheter and was deflated without sequelae.

Therapeutic implications of technique: Secundum atrial septal defects constitute approximately 10 percent of congenital heart defects and approximately 60 percent of them are reported to be central in location.[8] In the past, centrally located atrial septal defects of sufficient size (that is, with a pulmonary to systemic flow ratio of 1.5–2:1 or greater) have ultimately been treated with open heart closure. Rarely, in early infancy an isolated secundum atrial septal defect is associated with congestive heart failure.[9] Patients with this condition usually respond well to medical management and infrequently require surgical intervention at an early age. For such patients this technique of measuring the defect may become useful in corroborating clinical data to document changes in size and possible spontaneous closure.

This measuring technique also may prove useful in evaluating septectomy, such as the Blalock-Hanlon operation, or balloon septostomy used as palliation for transposition of the great vessels. In evaluating atrial septal defects associated problems may be suspected

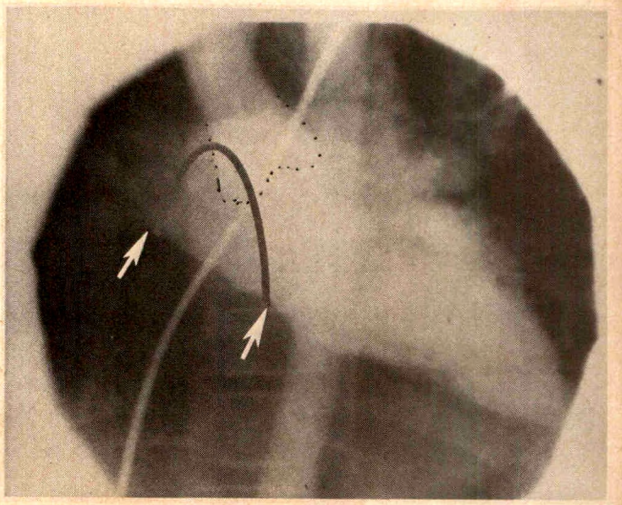

FIGURE 5. Frame from an anteroposterior pulmonary arterial cineangiocardiogram in the levogram phase showing the relation of the aortic valve to the atrial septum. The interatrial septum is in the plane encompassed by the semicircle, the base of which is indicated by **arrows. Dots** indicate the aortic valve and proximal ascending aorta. The catheter is in the pulmonary artery.

from data obtained. If the calculated left to right shunt is large (for example, 4:1) and the balloon-measured diameter of the atrial septal defect is small (for example, 10 mm), then anomalies such as abnormal pulmonary venous connections must be sought for.

Determining location of defects (differentiation from ostium primum defect): Closure of a central secundum atrial septal defect by nonoperative means[4,5] requires careful evaluation of the defect. Because the technique described permits more accurate estimation of the location of the defect, it can prevent risks involved in attempted closure of an ostium primum or sinus venosus defect. In 1 to 2 percent of cases, an ostium primum defect has a right axis deviation and clockwise loop. Therefore, if the gooseneck deformity of the cushion defect is not readily apparent on cineangiography, a primum anomaly can be mistaken for a secundum defect. Measurement of the distance from the mitral valve to the inferior septal rim obviates this error (Fig. 4, left). The technique described makes possible accurate sizing and precise localization of an atrial septal defect, two prime considerations in determining the feasibility for transvenous closure.

Surgical implications: Because we believe that we do not yet know the exact measurement in millimeters of an atrial septal defect that should be surgically closed, we still rely on the pulmonary to systemic flow ratio and left cineangiography for the first estimate of defect size. With increased experience, it is possible that balloon measurement may become a prime factor in determining the natural history and surgical significance of secundum atrial septal defects.

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Echocardiographic Assessment of Left Ventricular Outflow Tract in d-Transposition of the Great Arteries

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The left ventricular outflow tract in 38 patients (aged 0.3 to 13 years) with complete d-transposition of the great arteries, 31 with intraatrial (Mustard) repair, was quantitated with echocardiography, and the findings were correlated with hemodynamic and angiographic data. The left ventricular outflow tract (LVO) was measured on the echocardiogram as an antero-posterior dimension between the closure point on the mitral valve below the pulmonary arterial root (PA) and the left endocardial surface of the interventricular septum. This measurement was expressed as an LVO/PA ratio and on the basis of these measurements three groups were recognized.

Group I consisted of 14 patients who had an unobstructed left ventricular outflow tract and no significant pressure differences between the pulmonary artery and left ventricle. In Group II, the 16 patients had evidence of dynamic obstruction and mild to moderate pressure differences between the pulmonary artery and left ventricle, characterized in the echocardiogram by LVO/PA ratios comparable with those of Group I, but with an abnormally prominent early posterior systolic septal bulge in the left ventricular outflow tract, abnormal systolic anterior motion of the mitral valve and coarse fluttering of the pulmonary valve. In Group III the eight patients had anatomically fixed stenosis of the left ventricular outflow tract and severe left ventricular outflow pressure gradients characterized in the echocardiogram by a reduced LVO/PA ratio and fine vibrations of the pulmonary valve. Angiographically discrete or long segmental narrowing of the left ventricular outflow tract correlated well with the echocardiographic data. Echocardiographic measurements of left ventricular posterior wall thickness also correlated well with the severity of left ventricular outflow stenosis in these three groups. The echocardiogram provides clinically useful quantitative and qualitative analysis of the left ventricular outflow tract in patients with complete transposition of the great arteries.

The left ventricular outflow tract in patients with complete d-transposition of the great arteries may have anatomic or functional obstruction that results in a systolic pressure gradient between the left ventricle and the pulmonary artery. Fixed short or long segmental stenosis of the left ventricular outflow tract is caused by a relatively rigid fibrous or fibromuscular ridge or tunnel, whereas a dynamic or functional stenosis appears to be the result of abnormal systolic posterior bulging of the interventricular septum,[1] usually associated with abnormal systolic anterior movement of the mitral valve. Because the mortality rate of corrective surgery in patients with subpulmonary stenosis of the left ventricle is significantly higher than in uncomplicated cases and the relief of the stenosis is not always adequate,[2,3] accurate qualitative and quantitative assessment is important both for selection of the type of corrective surgery and for postoperative evaluation.[4]

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TABLE I

Echocardiographic and Hemodynamic Data of 38 Patients With Transposition of Great Arteries and Control Group

	Group I No LVO Stenosis (no. = 14)	Group II Dynamic Stenosis (no. = 16)	Group III Fixed Stenosis (no. = 8)	Control Subjects (no. = 42)
BSA (m^2)	0.80 ± 0.03	0.78 ± 0.18	0.73 ± 0.41	0.77 ± 0.40
LVO (cm)	1.7 ± 0.39	1.6 ± 0.30	0.7 ± 0.18	
LVO (cm/m^2)	2.15 ± 0.42	1.99 ± 0.33	1.22 ± 0.57	2.46 ± 0.42
PA (cm)	2.26 ± 0.6	2.10 ± 0.4	1.60 ± 0.5	
PA (cm/m^2)	2.83 ± 0.66	2.64 ± 0.44	2.67 ± 0.82	
LVO/PA ratio	0.77 ± 0.12	0.76 ± 0.12	0.44 ± 0.10	0.88 ± 0.06*
h (cm/m^2)	0.62 ± 0.17	0.75 ± 0.17	1.20 ± 0.43	
h/r ratio	0.29 ± 0.05	0.43 ± 0.11	0.61 ± 0.10	
LVOPSG (mm Hg)	8.3 ± 4.6	23.2 ± 12.9	76.7 ± 22.6	

* Left ventricular outflow tract/aorta ratio in control subjects.

BSA = body surface area; h = end-diastolic left ventricular posterior wall thickness; LVO = left ventricular outflow tract; LVOPSG = peak systolic pressure difference between left ventricle and the main pulmonary artery; PA = pulmonary arterial root; r = one half the end-diastolic left ventricular dimension.

Assessment of the left ventricular outflow tract has primarily been made from angiographic and intracardiac pressure observations. Recently, Nanda et al.[5] described several echocardiographic features of left ventricular outflow tract stenosis in patients with d-transposition of the great arteries; however, these echocardiographic findings were not quantitatively correlated with the angiographic or hemodynamic data. In this study we used echocardiographic measurements to describe quantitatively the various types of left ventricular outflow tract stenosis in patients with d-transposition and correlated the echocardiographic, angiographic and hemodynamic observations.

Materials and Methods

Patients: Thirty-eight patients with complete d-transposition of the great arteries were studied with echocardiography and cardiac catheterization, including angiography (Table I). Their ages ranged from 0.3 to 13 years. Fourteen patients had an associated ventricular septal defect, and the remaining 24 had an intact ventricular septum. Seven had no intracardiac surgery. Thirty-one patients had intraatrial corrective surgery with the Mustard procedure including eight who had closure of a ventricular septal defect and two who had resection of the left ventricular outflow tract obstruction. None of these patients had abnormally increased pulmonary vascular resistance.

Echocardiography: The echocardiographic examination was performed during cardiac catheterization in 16 of the 38 patients, and within 3 months of catheterization in the others. Left ventricular and pulmonary arterial pressure measurements, and selective left and right ventricular angiocardiograms were obtained in each patient.

The echocardiograms were recorded with a Smith-Kline Ekoline 20A echocardiograph interfaced with a Honeywell 1856 recorder. A 2.5 megahertz transducer focused at 5 cm was used in older children and an appropriate higher frequency transducer, 3.5 or 5 megahertz, was used in younger infants.

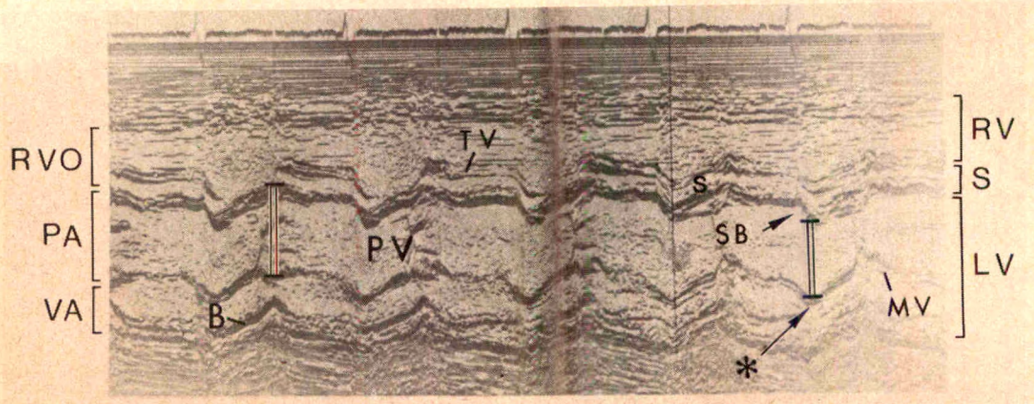


FIGURE 1. Echocardiographic scan from the pulmonary artery (PA) to the left ventricle (LV) in a patient with transposition of the great arteries with intact ventricular septum and unobstructed left ventricular outflow tract (Group I). Note the parallel alignment of the pulmonary artery to the interventricular septum (S), a prerequisite for valid quantification of the left ventricular outflow tract (LVO). The left ventricular outflow tract is measured as an anteroposterior dimension **(white bars*)** between the first recognizable closure point of the mitral valve and the left ventricular endocardial surface of the septum. The pulmonary artery is measured as an anteroposterior dimension **(white bars)** between the outer edges of the anterior and posterior vessel wall at end-systole. The size of the left ventricular outflow tract is expressed as an LVO/PA ratio. Note the modest posterior systolic bulge of the interventricular septum (SB). B = interatrial baffle; MV = mitral valve; PV = pulmonary valve; RV = right ventricle; RVO = right ventricular outflow tract; TV = tricuspid valve; VA = venous atrium.

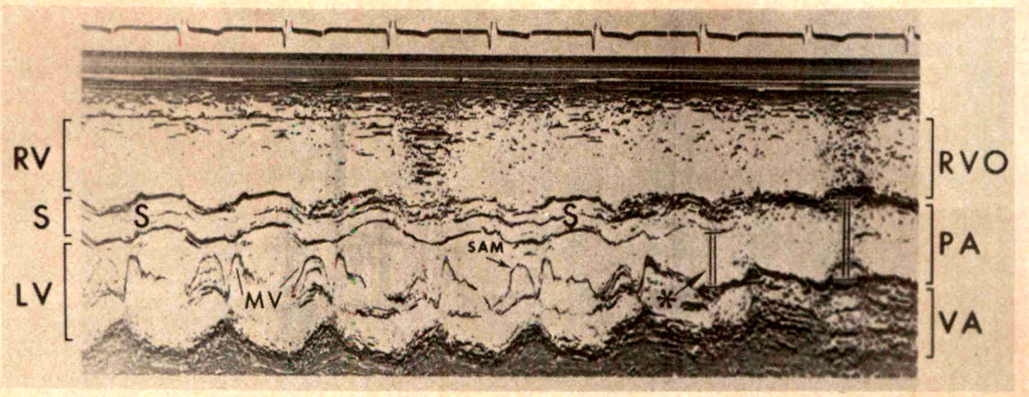


FIGURE 2. Characteristic echocardiographic features of dynamic obstruction of the left ventricular outflow tract (Group II) in a patient with transposition of the great arteries and an intact ventricular septum. Note the anterior systolic motion of the mitral valve (SAM) and the posterior systolic bulging of the interventricular septum (S) causing systolic narrowing of the left ventricular outflow tract. However, comparison of the echocardiographic dimensions of the left ventricular outflow tract **(arrow*)** with the pulmonary arterial root (PA) indicates that the outflow tract is not anatomically stenosed. Abbreviations as in Figure 1.

With the transducer placed in the third to fifth intercostal space, multiple scans were obtained from the pulmonary arterial root to the left ventricle.[6]

Parallel alignment of the pulmonary artery to the interventricular septum was maintained on the tracing to avoid distortion of the left ventricular outflow tract and permit valid quantification of this region.

Measurements: The dimensions of the pulmonary artery were measured at the level of the pulmonary valve between the outer edges of the anterior and posterior walls at end-systole. The left ventricular outflow tract was measured as an anteroposterior dimension between the first recognizable closure point of the the mitral valve below the pulmonary arterial root and the left ventricular endocardium of the interventricular septum[7] (Fig. 1). The measurement used was an average obtained from three to four scans from the pulmonary artery to the left ventricle and was expressed as a ratio of the left ventricular outflow tract to pulmonary arterial root dimensions (LVO/PA). Left ventricular end-diastolic dimensions were measured between the septal and posterior wall endocardium at the level of the largest mitral valve complex and at the time of the R wave peak in the simultaneous electrocardiogram.[8] Posterior and septal wall thickness were measured at the same site and time.

The left ventricular posterior wall thickness was measured between the endocardium and the epicardium; thick pericardial echoes were excluded. The septal thickness was measured between the right and left ventricular endocardial surfaces. The posterior systolic motion (septal bulge) of the interventricular septum in early systole was measured both at the exit of the left ventricular outflow tract just below the pulmonary arterial root and at the proximal left ventricular outflow tract inlet near the junction of the outflow and the left ventricular body. This latter level was established echocardiographically from the distinctive mitral valve tracing indicating proximity to the level of the mitral anulus. The septal bulge of the interventricular septum was measured from the left ventricular endocardium at end-diastole (peak of R wave) to the most posterior position reached during systole. The posterior wall thickness (h) was expressed as an index of body

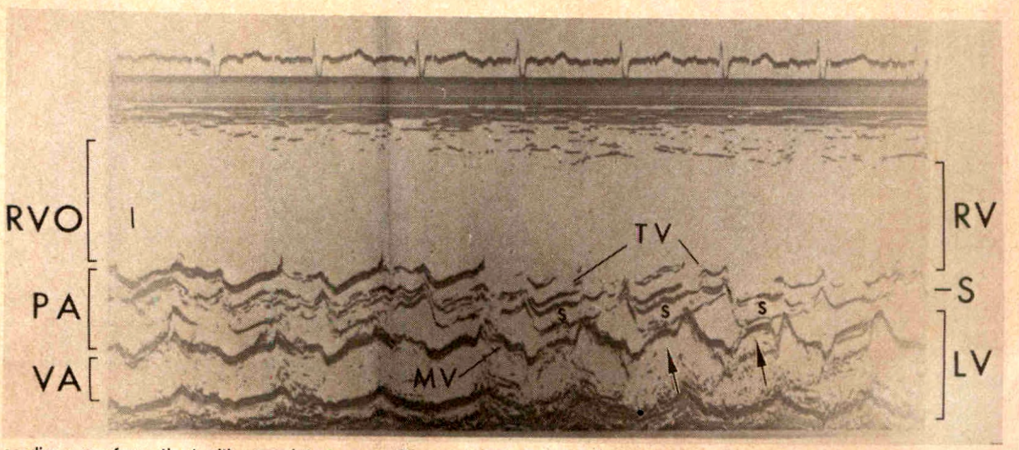


FIGURE 3. Echocardiogram of a patient with complete transposition and an intact ventricular septum illustrating dynamic stenosis of the left ventricular outflow tract. The extent of the posterior systolic bulge of the interventricular septum (S) progressively increases in the scan from the exit to the inlet portion of the left ventricular outflow tract. Systolic apposition of the septal bulge and the anterior mitral valve leaflet produces obliteration **(arrows)** of a portion of the left ventricular outflow tract. Abbreviations as in Figure 1.

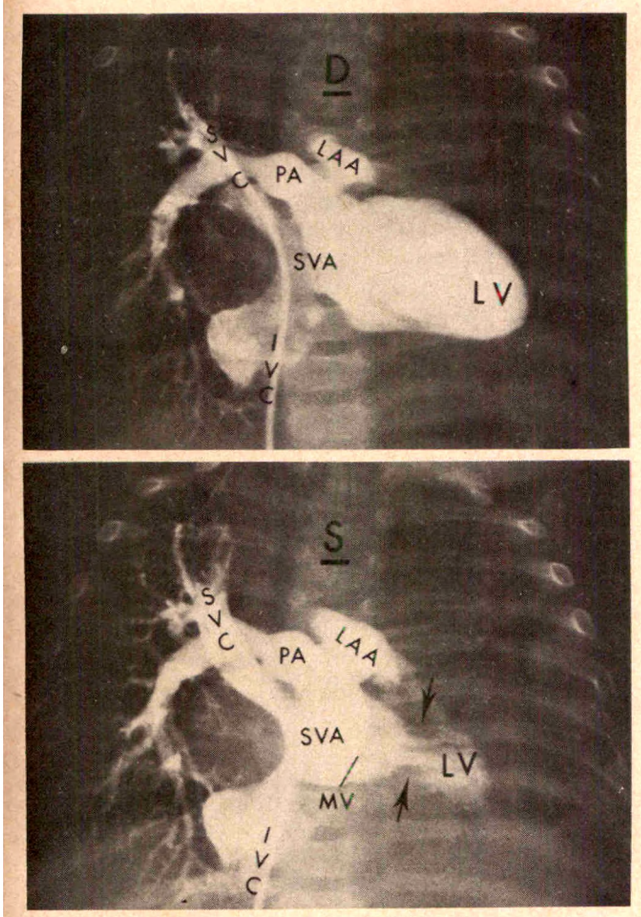


FIGURE 4. Same patient as in Figure 3. Diastolic (D) and systolic (S) phases of left ventricular angiogram (anteroposterior view) illustrating systolic cavity obstruction **(arrows)** with septal bulge. IVC = inferior vena cava; LAA = left atrial appendage; LV = left ventricle; MV = mitral valve; PA = pulmonary artery; SVA = systemic venous atrium; SVC = superior vena cava.

surface area in order to normalize this measurement for various ages. The effect of the left ventricular outflow stenosis on the posterior wall thickness was assessed by calculating the h/r ratio, where r is half the end-diastolic anteroposterior left ventricular dimension. This ratio has been shown to increase with increasing severity of the left ventricular outflow stenosis in patients with aortic stenosis.[9]

Forty-two subjects with normally related great arteries, 21 with a functional murmur and 21 with patent ductus arteriosus or ventricular septal defect shunting lesions had left ventricular outflow (LVO) tract and aortic (Ao) root dimensions measured and expressed as LVO/AO ratio. These measurements were made to establish control data for evaluation of the left ventricular outflow tract and the LVO/PA ratio in patients with transposition. No significant differences were noted in LVO/AO ratio between the control subjects with functional murmurs and the control subjects with shunting lesions.

Results

Three groups of patients can be recognized (Table I) from the echocardiographic measurements of the left ventricular outflow tract.

Group I (no obstruction): This group comprised 14 patients, 5 with a ventricular septal defect. All 14 patients had a Mustard (intraatrial) repair with closure of the ventricular septal defect when present. The echocardiograms of patients in this group were characterized by a relatively normal left ventricular outflow tract (Fig. 1). The left ventricular outflow tract to pulmonary arterial ratio (LVO/PA) was 0.77 ± 0.12 (mean ± standard deviation) compared with 0.88 ± 0.06 in the control subjects. At cardiac catheterization insignificant peak systolic pressure differences were recorded across the left ventricular outflow tract between the left ventricle and the main pulmonary artery (8.3 ± 4.6 mm Hg). The pulmonary and mitral valves did not manifest any abnormal movements in systole. A small degree of septal bulge was noted in the distal left ventricular outflow

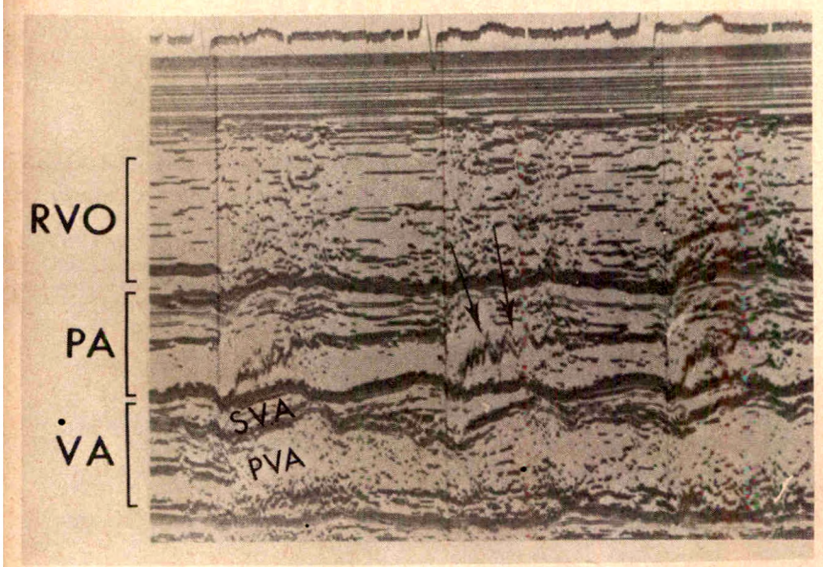
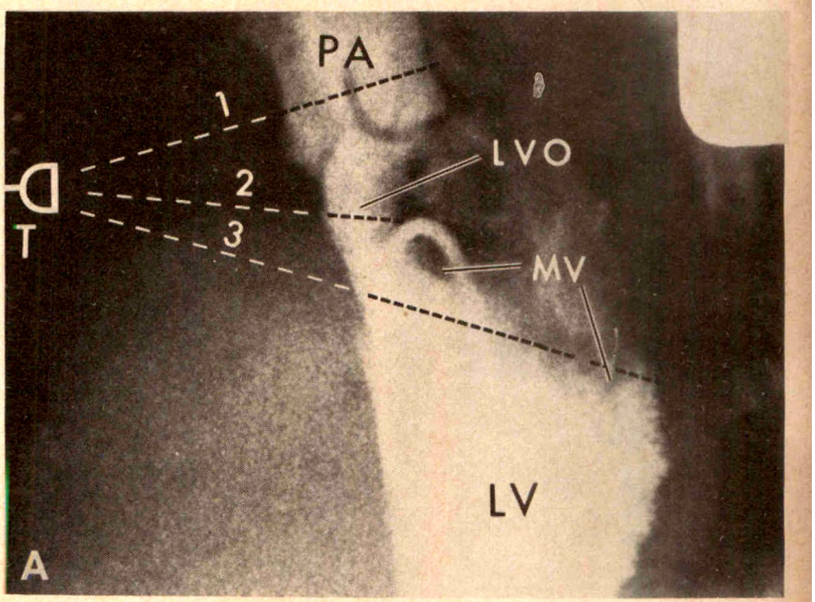


FIGURE 5. Echocardiogram illustrating coarse systolic fluttering of the posterior leaflet of the pulmonary valve **(arrows)** in a patient with transposition and dynamic obstruction of the left ventricular outflow tract. PVA = pulmonary venous atrium; SVA = systemic venous atrium. Other abbreviations as in Figure 1.

tract (0.26 ± 0.11 cm); the septal bulge was somewhat more prominent proximally at the junction of the outflow tract and the left ventricular body (0.34 ± 0.08 cm). The left ventricular posterior wall was not hypertrophied (0.49 ± 0.15 cm; 0.62 ± 0.17 cm/m^2) compared with that in the groups with outflow obstruction (Group II, 0.57 ± 0.12 cm; 0.75 ± 0.17 cm/m^2 and Group III, 0.71 ± 0.16 cm; 1.20 ± 0.43 cm/m^2). Group I patients also had no angiographic evidence of left ventricular outflow tract obstruction.

Group II (dynamic type of left ventricular stenosis): Of the 16 patients in this group, 2 had a ventricular septal defect and 15 had a previous intraatrial Mustard repair and closure of the ventricular septal defect when present. The echocardiograms in this group were characterized by an anatomically unobstructed left ventricular outflow tract with an LVO/PA ratio of 0.76 ± 0.12, essentially identical to that of Group I (Table I). However, an abnormal systolic anterior motion of the mitral valve and more prominent posterior septal bulge were present in all patients (Fig. 2). These abnormalities were associated with mild to moderate pressure differences recorded between the left ventricle and pulmonary artery (23.2 ± 12.9 mm Hg).

The posterior septal bulge at the distal or exit level of the left ventricular outflow was more prominent in Group II than in Group I: 0.36 ± 0.10 versus 0.26 ± 0.10 cm. This difference was much greater at the proximal or inlet level (Fig. 3); 0.53 ± 0.14 cm in Group II versus 0.34 ± 0.08 cm in Group I. Patients in Group II also



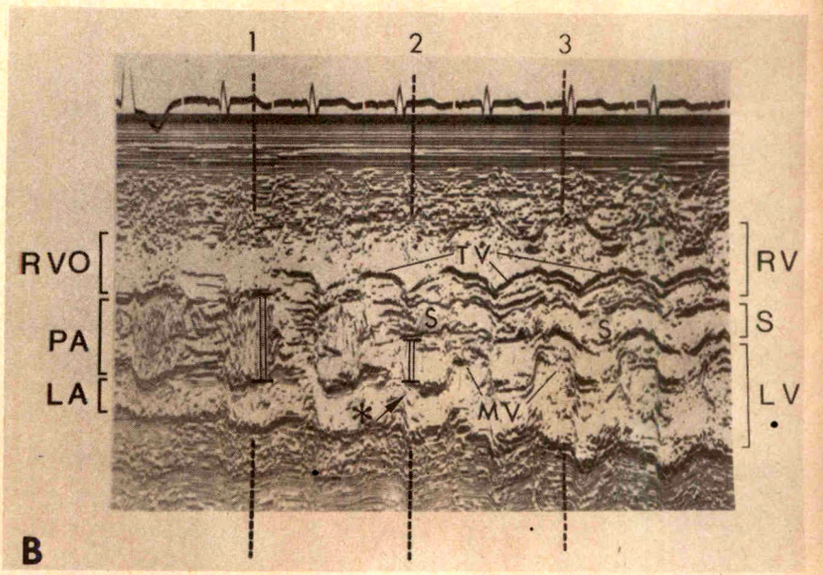


FIGURE 6. A patient with transposition and intact ventricular septum (Group III). **A,** left ventricular angiogram (left lateral view) illustrating fixed segment of stenosis of the left ventricular outflow (LVO) tract at scan position 2. T = transducer. **B,** echocardiogram demonstrating a narrowed left ventricular outflow tract dimension (*) at scan position 2 compared with the pulmonary arterial root (PA) dimension at scan position 1. There is echocardiographic contrast material in the pulmonary artery. Abbreviations as in Figure 1.

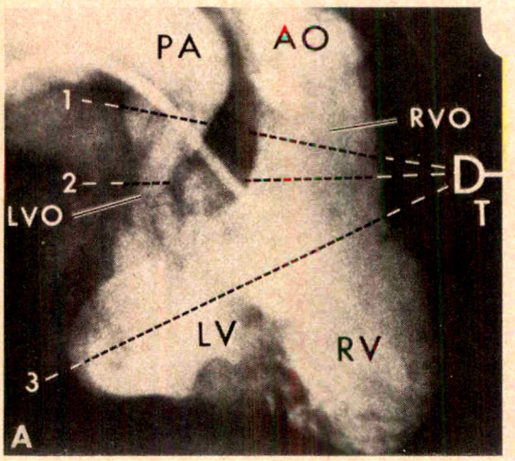
manifested greater hypertrophy of the left ventricular posterior wall, reflecting a higher left ventricular pressure in this group (Table I). In two patients systolic apposition of the posteriorly bulging interventricular septum and anteriorly displaced mitral valve was recorded in the echocardiogram (Fig. 3), and the angiocardiogram (Fig. 4) showed moderate to severe systolic septal bulging and systolic cavity obliteration. The angiocardiograms of patients in Group II were characterized by moderate to marked systolic septal bulging with normal left ventricular outflow tract dimensions. In high speed cineangiograms abnormal systolic anterior motion of the mitral valve could be recognized with careful examination in 7 of the 16 patients in this group. Coarse systolic fluttering of the pulmonary valve (Fig. 5) as well as mid systolic closure of either the anterior or posterior leaflet was observed in 10 of 16 patients in Group II. One patient with echocardiographic features of dynamic stenosis also showed a relative narrowing of the left ventricular outflow tract (LVO/PA ratio, 0.60) and thus had the additional diagnosis of fixed stenosis (Group III).

Group III (anatomically fixed) left ventricular stenosis: Of the eight patients in this group, seven had a ventricular septal defect. Three patients had the Mustard operation, two had resection of the left ventricular outflow tract obstruction and closure of the ventricular septal defect and one had only closure of the defect.

The echocardiograms of these patients were characterized by a markedly narrowed left ventricular outflow tract (LVO/PA ratio 0.44 ± 0.10). This narrowing of the outflow tract correlated well with the angiocardiographic appearance (Fig. 6 to 8). The length of the narrowed segment was suggested by the echocardiographic scans to some extent, and in a few patients the presence of a ventricular septal defect was established by the interruption of the septal echoes under the pulmonary arterial root (Fig. 8B). Pulmonary arterial alignment to the left ventricle could be ascertained in all patients. The left ventricular pressures were elevated to systemic or suprasystemic levels and the left ventricular posterior wall was hypertrophied compared with that in the patients without obstruction (Group I) or in those with dynamic stenosis (Group II) (Table I). Systolic anterior motion of the mitral valve was not observed in any patient in Group III; however, fine high frequency systolic vibrations of the pulmonary valve were noted in six of the 8 patients (Fig. 9).

Discussion

This study illustrates that several qualitative and quantitative echocardiographic observations can be



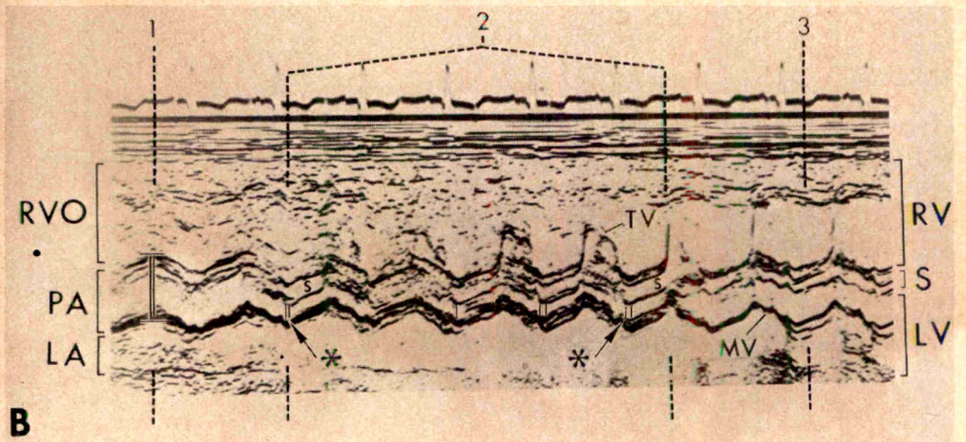
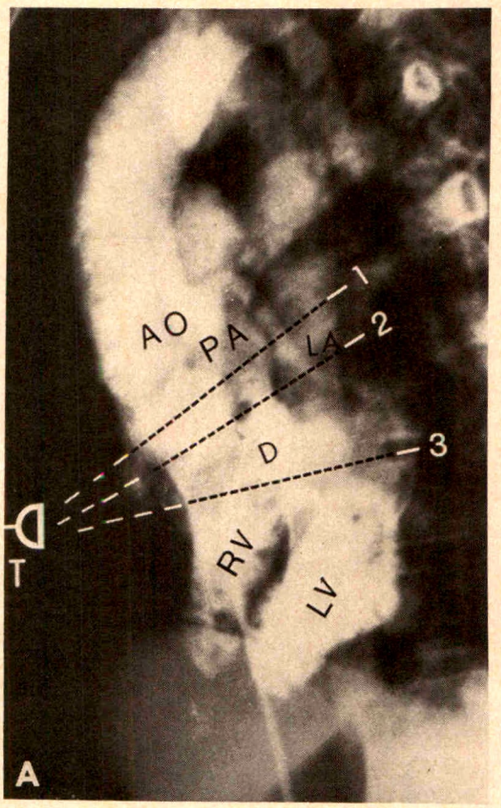


FIGURE 7. A patient with transposition and ventricular septal defect (Group III). **A,** right ventricular angiogram (right lateral view) showing a segmental narrowing of the left ventricular outflow tract (LVO) at scan position 2. **B,** echocardiogram demonstrating a long segment of outflow tract (*) narrowing in scan position 2.

used to distinguish among various types of left ventricular outflow tract stenosis in patients with complete transposition of the great arteries. Patients with an anatomically and functionally unobstructed left ventricular outflow tract with insignificant pressure differences across the outflow tract can be separated from patients with stenosis of the outflow tract and significant pressure differences. Furthermore, patients whose outflow tract manifests anatomically fixed subpulmonary stenosis can be separated from those with a dynamic type of stenosis, but our data are insufficient to define the degree of overlap between these two groups. However, the echocardiogram did suggest a dual lesion in at least one of our patients. These two echocardiographically characterized types of left ventricular outflow tract obstruction correlated well with the angiographic appearances. Increased left ventricular pressure due to either fixed or dynamic stenosis resulted in increased left ventricular hypertrophy as assessed from posterior wall thickness. This echocardiographic



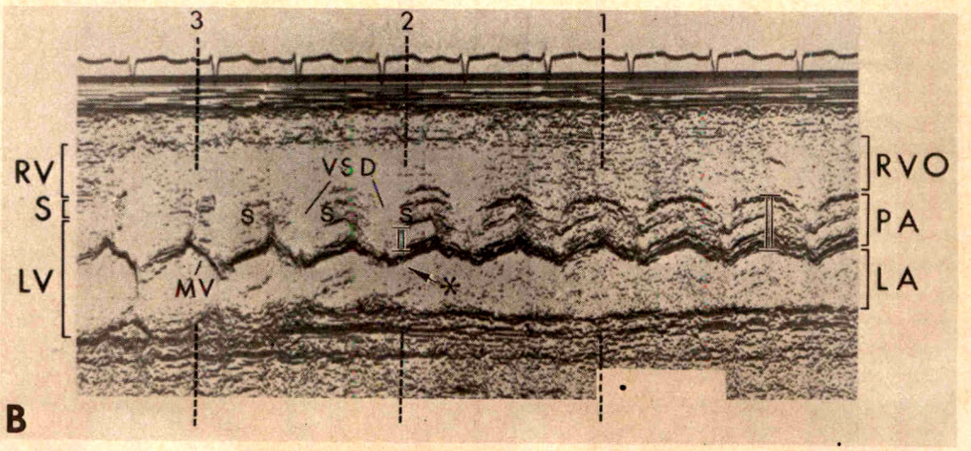


FIGURE 8. A patient with transposition and ventricular septal defect (D). **A,** left ventricular angiogram (left lateral view) showing outflow tract stenosis at scan position 2. **B,** echocardiogram demonstrating a significantly narrowed left ventricular outflow tract dimension (*) at scan position 2 compared with the pulmonary arterial root dimension. The position of the ventricular septal defect (VSD) is indicated by the interrupted septal echoes. LA = left atrium; other abbreviations as in Figure 1.

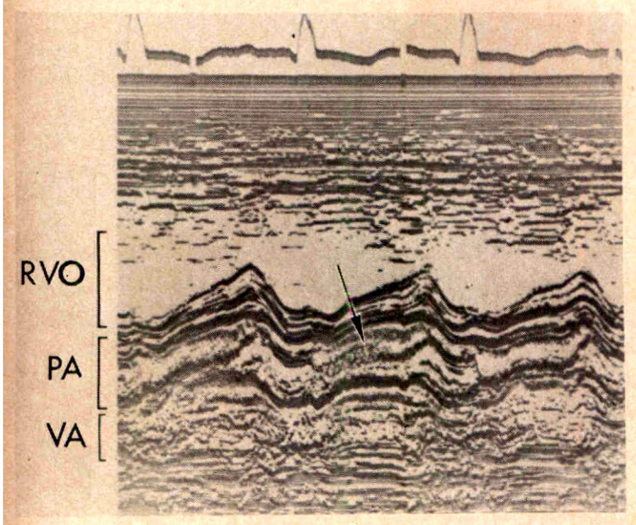


FIGURE 9. Echocardiogram from a patient with transposition and fixed left ventricular outflow tract stenosis (Group III) illustrating high frequency systolic vibrations of a pulmonary valve leaflet **(arrow).** Abbreviations as in Figure 1.

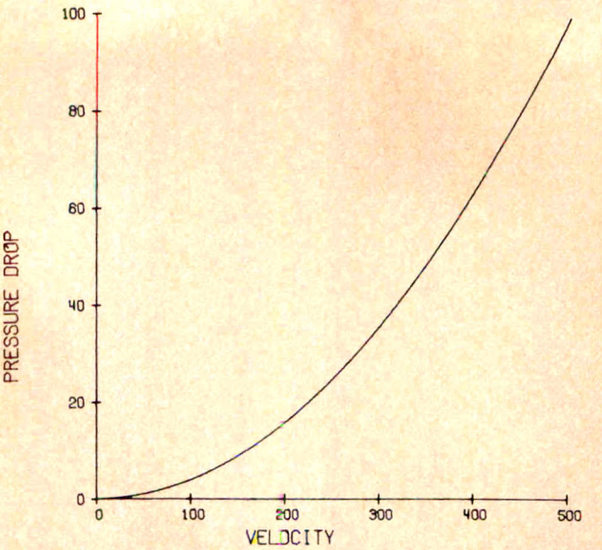


FIGURE 10. Calculated relation of pressure loss (mm Hg) **(ordinate)** to the blood flow velocity (cm/sec) **(abscissa)** resulting from conversion of pressure into kinetic energy (kinetic energy = $\frac{1}{2} \rho v^2$; where ρ = density and v = velocity of blood). Note that a two- or three-fold increase in blood flow velocity results in a significant local reduction in pressure downstream from the septal bulge in the left ventricular outflow tract inlet region. This reduction could influence the dynamics of mitral valve movement and induce abnormal systolic anterior movement.

finding also clearly separated the group of patients without obstruction with relatively low left ventricular systolic pressures from those with significant left ventricular outflow tract stenosis.

Dynamic left ventricular stenosis in transposition: Although systolic posterior septal bulging occurs to some extent in all patients with transposition of the great arteries, dynamic stenosis, that is, systolic narrowing of the left ventricular outflow tract, seems to be caused by exaggerated posterior septal bulging in concert with abnormal systolic anterior motion of the mitral valve. Nanda et al.[5] suggested that a form of asymmetric septal hypertrophy with systolic anterior motion of the mitral valve similar to idiopathic hypertrophic subaortic stenosis could be responsible for dynamic stenosis. In our patients with dynamic stenosis we found no evidence of asymmetric septal hypertrophy, and the septal and posterior walls were of essentially equal thickness.

Our observations indicate that the mechanism of dynamic stenosis is related to abnormally prominent systolic posterior septal bulging and systolic anterior motion of the mitral valve. They support recent angiocardiographic observations illustrating the abnormal anterior systolic displacement of the mitral valve toward a posterior systolic septal bulge.[10] In two of our patients the septal bulge was great enough to cause systolic mid cavity obliteration. A prominent septal bulge was previously reported in pathologic and angiocardiographic studies of patients with transposition [1,10,11] as contributing to left ventricular outflow tract stenosis. The mechanism of systolic anterior motion of the mitral valve remains conjectural and seems to be dependent upon altered left ventricular configuration and abnormal fluid hydraulics. It can be postulated that if the left ventricular outflow dimensions are significantly narrowed by the systolic posterior bulging of the interventricular septum, a sufficiently increased velocity of flow may be generated to initiate abnormal systolic anterior motion of the mitral valve. This would occur because of a downstream pressure loss below the pulmonary artery resulting from conversion of pressure into kinetic energy (Bernoulli effect) (Fig. 10). Furthermore, the commonly observed coarse fluttering of the pulmonary valve (Fig. 5) in these patients with dynamic stenosis may indeed represent a downstream reflection of rapidly altering blood flow velocities resulting from a gating mechanism at the site of apposition of the mitral valve and interventricular septum.

Anatomically fixed left ventricular outflow stenosis in transposition: In contrast to dynamic stenosis, fixed stenosis is distinguished echocardiographically by a narrowing that persists during the systolic and diastolic phases of the cardiac cycle. The restricted left ventricular outflow tract produces high velocity flow, which may be responsible for the high frequency vibrations of the pulmonary valve noted in these patients. Furthermore, the resultant increase in left ventricular peak systolic pressure results in the left ventricular hypertrophy.

Implications: Our findings indicate that with the echocardiogram one can, by using several measurements, distinguish between dynamic and fixed obstructive types of left ventricular outflow tract stenosis in patients with transposition of the great arteries. These measurements include (1) quantitative mea-

surements of the left ventricular outflow tract and, in particular, the LVO/PA ratio; (2) analysis of systolic interventricular septal and mitral valve motion; (3) quantitation of left ventricular posterior wall thickness; and (4) analysis of systolic pulmonary valve vibrations. Furthermore, pre- and postoperative longitudinal assessment of these forms of left ventricular outflow tract stenosis in patients with transposition appear to be feasible with use of this noninvasive technique.

Acknowledgment

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His Bundle Electrogram After Intracardiac Repair of Tetralogy of Fallot

Analysis of Data in 59 Patients

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His bundle electrograms were recorded in 59 patients after intracardiac repair of tetralogy of Fallot and were correlated with the postoperative electrocardiogram. Except for five patients with first degree atrioventricular block postoperatively all patients in Group A (those with either a normal electrocardiogram or solitary right bundle branch block) had a normal A-H interval (77.7 ± 21.6 msec) (mean ± standard deviation); all had a normal H-V interval (39.5 ± 7.2 msec). Patients in Group B (bifascicular block) tended to have a normal A-H interval (97.2 ± 26.2 msec) with a prolonged H-V interval (48.8 ± 10.7 msec). Patients in Group C (trifascicular block) had prolongation of both the A-H (160.0 ± 32.4 msec) and the H-V interval (58.8 ± 10.6 msec) by comparison with control values. Patients in Group D (transient complete heart block) had a normal A-H interval (79.5 ± 28.2 msec) but a prolonged H-V interval (57.8 ± 16.4 msec), similar to that in Group C. A good hemodynamic result was associated with a normal H-V interval; a prolonged interval accompanied a poor result.

Abnormalities in atrioventricular (A-V) conduction are known to occur after intracardiac repair of tetralogy of Fallot. Postoperatively, the majority of patients have a right bundle branch block pattern in the surface electrocardiogram[1]; 8 to 22 percent manifest bifascicular block[2–12] and 4 percent the electrocardiographic pattern of trifascicular block.[12] Within recent years only a small group, 1 to 2 percent, have shown complete heart block.[13,14] The reported consequences of these A-V conduction abnormalities vary. In one series,[4] the mortality related to cardiac arrhythmias was 25 percent (6 of 24) in patients with bifascicular block after surgery; in other series the investigators[11,12] were unable to relate bifascicular block and poor outcome although in one report[12] trifascicular block resulted in a 30 percent incidence rate of sudden death (3 of 10). In yet another group[2] sudden death occurred in 3 percent (4 of 181) of patients without bifascicular block but with exercise-induced ventricular ectopy. Complete heart block is usually associated with a poor outcome,[13] may develop a number of years after operation[14] and usually requires a permanent pacemaker.[14] Thus, A-V conduction abnormalities appear to affect prognosis after repair of tetralogy of Fallot. To determine the extent of surgically induced A-V conduction abnormalities and their relation to the surface electrocardiogram, hemodynamic results and outcome, we obtained His bundle electrograms from 59 patients after repair of tetralogy of Fallot.

Material and Methods

Patients: Sixty postoperative patients with tetralogy of Fallot were evaluated at routine follow-up cardiac catheterization. One patient was excluded from the study because of severe subaortic stenosis. The remaining 59 patients evaluated between April 1, 1974 and June 30, 1976 represent a consecutive series of patients who had a technically satisfactory His bundle electrogram after repair of

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tetralogy of Fallot. Thirty-three of the patients were studied within 2 years of operation. Fourteen preoperative patients, 12 with tetralogy of Fallot (median age 7 11/12 years), served as control subjects.

Electrocardiograms: The pre- and postoperative electrocardiograms of all 59 postoperative patients were examined. No patient had right bundle branch block preoperatively (rSR′ in lead V_1, a deep slurred S wave in leads I and V_6 and QRS duration of 0.12 second or more).[10,15] All patients had right ventricular hypertrophy and 56 had right axis deviation before operation. Three patients in Group A but none in Groups B, C or D had a leftward superior frontal plane electrocardiographic axis preoperatively. After operation six patients did not meet the criteria for right bundle branch block (including rate-related prolongation of the QRS interval); in four of these six there was no change in QRS configuration or duration, and in two the QRS interval lengthened by 0.03 second but not sufficiently to permit the diagnosis of right bundle branch block.

Classification of postoperative electrocardiograms: The 59 patients were then classified according to postoperative electrocardiographic findings. *Group A* comprised 44 patients with either normal intraventricular conduction or right bundle branch block. *Group B* consisted of five patients with bifascicular block (right bundle branch block and left anterior hemiblock [superior frontal plane axis of −30° or less, with a counterclockwise loop]).[15] The five patients in *Group C* manifested the electrocardiographic pattern of trifascicular block postoperatively (bifascicular block and first degree A-V block). One of the five (Case 2) also had transient complete heart block. *Group D* was composed of four patients with transient complete heart block (recorded in the intensive care unit and persisting for not more than 3 weeks postoperatively). An additional patient (Case 15) had transient bifascicular block postoperatively lasting 10 days,[16] but at follow-up study manifested right bundle branch block, first degree A-V block and a clockwise frontal plane loop in the vectorcardiogram. The postoperative electrocardiographic changes in all four groups were observed shortly after operation in the intensive care unit (maximal interval 6 months in Patient 14) and did not change thereafter except in Patient 15 and in all patients in Group D, who had reversion to intact A-V conduction.

Cardiac catheterization studies and His bundle recordings: These were performed with patients in the postabsorptive state under light sedation with an intramuscular injection of meperidine (2 mg/kg, not exceeding 50 mg), promethazine hydrochloride (0.25 mg/kg, not exceeding 12.5 mg) and chlorpromazine (0.25 mg/kg, not exceeding 12.5 mg). Digoxin, taken by 15 patients, was omitted on the morning of catheterization. Intracardiac electrode catheters were connected to a Hewlett-Packard bioelectric high input impedance differential amplifier (MN 8811A). His bundle electrograms were recorded through either bipolar or unipolar electrodes at a band width of 15 to 300 hertz with use of an optical writer on photographic paper moving at either 100 or 200 mm/sec.[17,18] A simultaneous lead II electrocardiogram was also recorded. Appropriate intervals were measured in three or four beats and a mean value was derived. The A-H interval was measured from the onset of the A wave to the onset of the H deflection. The H-V interval was taken from the onset of the H deflection to the onset of either the V wave of the ventricular electrogram or the Q wave of the lead II electrocardiogram, whichever came first.[19]

The hemodynamic findings at cardiac catheterization were graded according to criteria modified from Ruzyllo et al.[20] *A good repair was defined as follows:* (1) no ventricular septal defect; (2) a peak systolic ejection gradient across the right ventricular outflow tract of 40 mm Hg or less or a peak right ventricular systolic pressure of 50 percent or less of systemic pressure,[2] or both. *A fair repair was defined as* (1) a residual ventricular septal defect with a pulmonary to systemic flow ratio of 1.5:1 or less; (2) a peak systolic ejection gradient across the right ventricular outflow tract of 60 mm Hg or less or a peak right ventricular systolic pressure of 75 percent or less of systemic pressure, or both. *A repair was considered poor if there were* (1) a residual ventricular septal defect with a pulmonary to systemic flow ratio greater than 1.5:1, and (2) a peak systolic ejection gradient across the right ventricular outflow tract greater than 60 mm Hg or a peak right ventricular systolic pressure greater than 75 percent of systemic pressure, or both. These three hemodynamic categories were correlated with the electrocardiographic groups.

Statistical analyses were carried out using Student's *t* test for grouped data.

Results

His bundle electrograms (Tables I and II, Fig. 1): The 14 control patients had a mean A-H interval of 84.4 ± 28 msec (± standard deviation) and an H-V interval of 35.8 ± 7.1 msec. These intervals are similar to normal values for age (Fig. 1).[21–24]

Patients in Group A generally had normal His bundle electrographic intervals; after correction for age and heart rate, the A-H interval was prolonged in five patients with first degree A-V block; in the remainder, it was normal (77.7 ± 21.6 msec). In all 44 patients in Group A the H-V interval was normal (39.5 ± 7.2 msec). Patients in both Groups B and D had an A-H interval not significantly different from that of the control group (97.2 ± 26.2 and 79.5 ± 28.2 msec, respectively). Patients in Group C had a prolonged A-H interval (160.0 ± 32.4 msec) that was nearly twice the value recorded in the control group and the other three groups. The H-V interval was significantly prolonged, by comparison with control values, in Groups B (48.8 ± 10.7 msec), C (58.8 ± 10.6 msec) and D (57.8 ± 16.4 msec).

One patient (Case 2) had both bifascicular block and transient complete A-V block but was included only in group B; he was 7 9/12 years old when he underwent correction of tetralogy of Fallot. In the operating room, transient complete A-V block appeared for several minutes. The His bundle recording 1 1/2 years later disclosed normal A-V conduction times of the A-H (65 msec) and H-V (46 msec) intervals. A second patient (Case 8) underwent initial repair at age 11 2/12 years. For several minutes while still in the operating room, he had transient complete heart block. After A-V conduction resumed in the intensive care unit, trifascicular block was noted in the surface electrocardiogram. At recatheterization 9 11/12 years later the His bundle electrogram disclosed a prolonged H-V interval (71 msec). He died at reoperation for a large residual ventricular septal defect and pulmonary stenosis at age 21 2/12 years. Patient 14 had transient complete heart block for 3 weeks after operation (age 11 10/12 years). At age 20 a His bundle study disclosed 2:1 H-V block (infra-His) at an atrial pacing rate of 125/min. Administration of atropine shortened A-H conduction slightly but did not alter the response of the H-V interval to atrial pacing. In Patient 9 an initial operation at age 9 9/12 years yielded a poor hemodynamic result and the electrocardiographic pattern of trifascicular block. Reoperation 2 years later for a residual ventricular septal defect and pulmonary stenosis resulted in a good hemodynamic repair and a normal H-V interval at rest. With atrial pacing at a rate of 110/min, 2:1 A-H A-V block

TABLE I

Summary of Data in Groups B, C and D

Case no.	Postoperative Electrocardiogram: P-R Interval (seconds)	QRS V_1 Pattern	QRS Axis Frontal Plane	Hemodynamic Result	Intervals: A-H (msec)	Intervals: H-V (msec)	Outcome	Right Atrial Pacing
			Group B (bifascicular block)					
1	0.14	RBBB	−90	Good	92	37	Alive	. . .
2	0.16	RBBB	−60	Poor	65	46	Alive	. . .
3	0.18	RBBB	−45	Fair	118	59	Alive	. . .
4	0.14	RBBB	−150	Poor	82	41	Alive	. . .
5	0.18	RBBB	−120	Good	129	61	Alive	. . .
			Group C (trifascicular block)					
6	0.22	RBBB	−100	Poor	153	67	Dead	. . .
7	0.22	RBBB	−100	Poor	166	55	Alive	. . .
8	0.26	RBBB	−90	Poor	121	71	Dead	. . .
9	0.22	RBBB	−90	P→G	150	44	Alive	Supra-His block
10	0.26	RBBB	−45	Poor	210	57	Alive	. . .
			Group D (transient complete heart block)					
11	0.18	RBBB	+120	Poor	63	57	Alive	. . .
12	0.14	RBBB	+90	Good	58	37	Alive	. . .
13	0.16	RBBB	+135	Good	77	60	. . .	. . .
14	0.18	RBBB	+90	Good	120	77	Alive	Infra-His block
			Other*					
15	0.18	RBBB	+210	Poor	89	142	Alive	

* This patient had transient bifascicular block postoperatively for 10 days but at follow-up study manifested right bundle branch block, first degree A-V block and a clockwise frontal plane loop in the vectorcardiogram.
P → G = poor after initial repair; good after reoperation.

(supra-His or within the A-V node) developed while the H-V interval remained constant. A fifth patient (Case 15) had transient bifascicular block for 10 days after an initial repair at age 7 4/12 years. Follow-up catheterization 11 months later revealed a large ventricular septal defect and pulmonary stenosis. The His bundle electrogram demonstrated an A-H interval of 86 msec and a markedly prolonged H-V interval of 142 msec (Fig. 2). Neither the scalar electrocardiogram nor the vectorcardiogram revealed bifascicular block. Reoperation was successful.

His bundle electrogram versus surface electrocardiogram: In this series, 60 percent (9 of 15) of the patients with postoperative electrocardiographic evidence of injury to the A-V conduction system (Groups B, C and D and one patient with transient bifascicular block) had a longer than age-related H-V interval (more than 55 msec in each case) (Fig. 1, Table II). In contrast, none of the 44 patients in Group A demonstrated comparable prolongation of the H-V interval. Specifically, two of five patients in Group B, three of five in Group C and three of four in Group D demonstrated a greater than normal age-related prolongation of H-V conduction time. In one additional patient the prolongation was at the upper limits of normal (Fig. 1). However, individual patients in Groups B, C and D (Table I) with H-V or A-H and H-V prolongation could not be reliably identified by examination of the surface electrocardiogram.

TABLE II

His Bundle Electrographic Intervals Related to Electrocardiographic Group

Group	Cases (no.)	Intervals (mean ± SD): A-H (msec)	Intervals (mean ± SD): H-V (msec)	*P* value*: H-V
Control	14	84.4 ± 28.0	35.8 ± 7.1	. . .
A	44	77.7 ± 21.6†	39.5 ± 7.2	NS
B	5	97.2 ± 26.2	48.8 ± 10.7	<0.05
C	5	160.0 ± 32.4	58.8 ± 10.6	<0.001
D	4	79.5 ± 28.2	57.8 ± 16.4	<0.02
Other	1	78	142	. . .

* Compared with value in control group.
† Five patients with first degree A-V block were excluded.
Groups defined as in text and Table I; NS = not significant; *P* = probability; SD = standard deviation.

H-V conduction related to age and surgical technique: To examine factors that might influence H-V conduction after intracardiac surgery we compared the ages of patients in the control group and the four electrocardiographic groups at the time of both His bundle study and surgery. Although there was no difference in age at the time of His bundle study between the control group and Groups A and B, patients in Groups C and D were significantly older ($P < 0.05$). Among Groups A, B and D, there were no significant differences in age at the time of cardiac catheterization or surgery; however, patients in Group C were significantly older ($P < 0.05$) at the time of catheterization but not at the time of surgery. Thus, age at the time of His

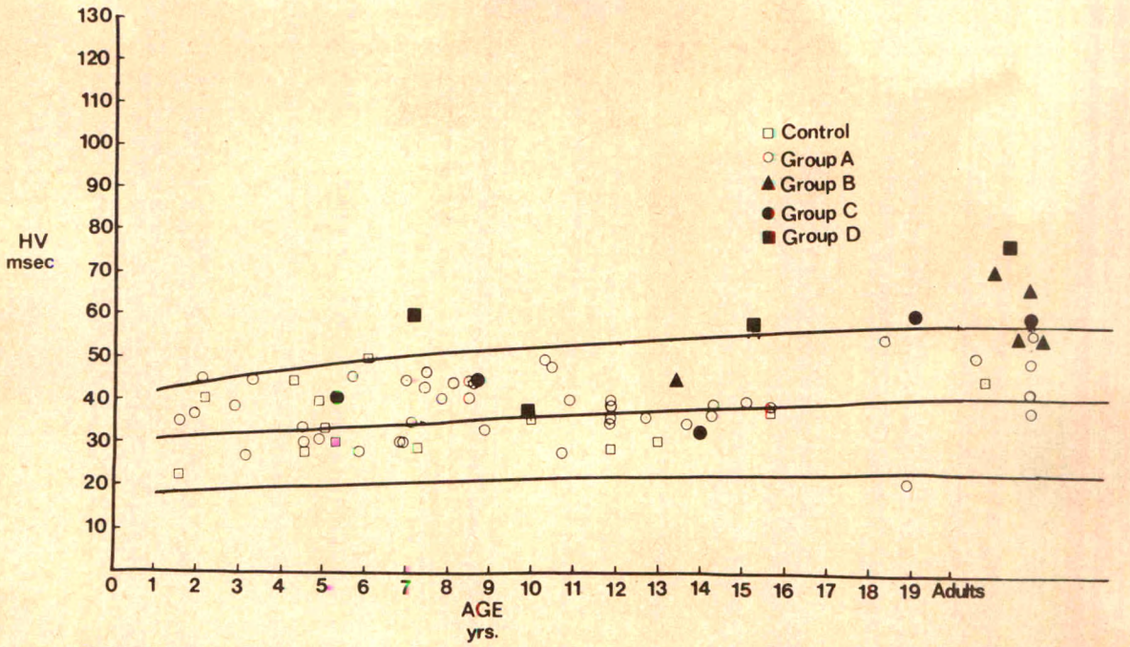

FIGURE 1. H-V interval (H-V) related to age at His bundle study in 59 study patients and 14 control patients.

bundle study may, in part, account for the prolonged H-V interval in Groups C and D, but not in Groups A and B. However, age at operation cannot be implicated because there was no significant difference in this factor among the four groups. In addition, to take into account improvement in surgical and perfusion techniques, we compared the H-V intervals of patients operated on before and after 1970; patients operated on from 1960 through 1969 had a significantly longer ($P < 0.05$, no. = 56) H-V interval (51.8 ± 15.7 msec) than patients operated on from 1970 through 1974 (41.5 ± 8.4 msec). Five of the 11 patients operated on before 1970 had a greater than normal age-related H-V interval, whereas only 2 of the 45 in the group operated on from 1970 through 1974 had a greater than age-related prolongation of H-V interval.

Correlation of electrophysiologic and hemodynamic results: Analysis of hemodynamic data revealed a good result in 53 percent of patients (31 of 59), a fair result in 17 percent (10 of 59) and a poor result in 31 percent (18 of 59). When electrocardiographic and hemodynamic data were correlated (Table III), 59 percent of patients in Group A had a good repair whereas approximately 20 percent had a fair and 20 percent a poor result. In contrast, only 33 percent (5 of 15) of the patients with either bifascicular or trifascicular block or transient complete heart block (Groups B, C and D) or transient bifascicular block (Other) had a good hemodynamic result. When hemodynamic results were correlated with the H-V interval (Table IV) an increasingly poorer surgical result was associated with progressive increases in the H-V interval. This finding was signifi-

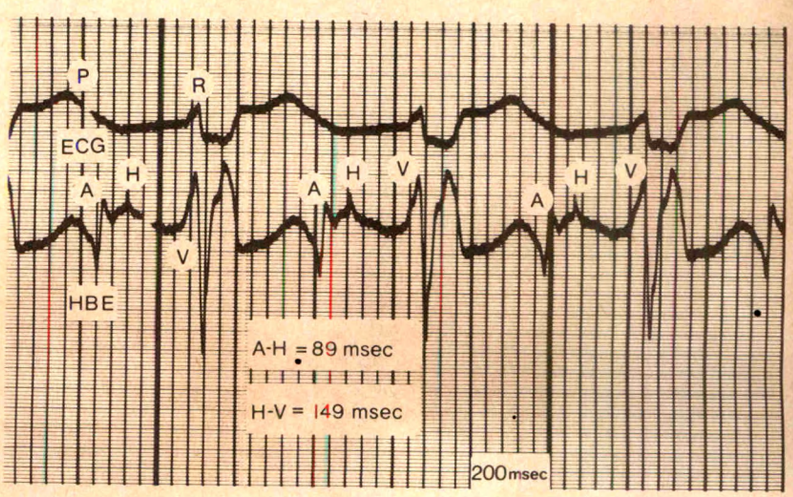

FIGURE 2. Case 15. Simultaneous lead II of the electrocardiogram and His bundle recording. Note the His deflection (H) during the isoelectric P-R interval and the prolonged H-V interval. A = atrial electrogram; ECG = electrocardiogram; H = His bundle electrogram; HBE = His bundle recording; P = P wave; R = R wave; V = ventricular electrogram.

TABLE III

Electrocardiographic Group Related to Hemodynamic Result

Electrocardiographic Group	Hemodynamic Result: Good no.	Good %	Fair no.	Fair %	Poor no.	Poor %
A	26	59	9	20	9	20
B	2	40	1	20	2	40
C	0	...	0	...	5	...
D	3	...	0	...	1	...
Other	...	...	0	...	1	...
Total	31	53	10	17	18	31

TABLE IV

Classification of H-V Intervals (msec; mean ± standard deviation) According to Hemodynamic Result and Electrocardiographic Group

Group	Hemodynamic Result: Good	Fair	Poor
A	37.0 ± 6.0 (no. = 26)	41.6 ± 7.0 (no. = 9)	45.3 ± 7.2* (no. = 9)
B, C, D	54.4 ± 17.3† (no. = 5)	58.0 ± 1.4‡ (no. = 2)	54.4 ± 11.5§ (no. = 7)

* $P < 0.01$ when compared with the H-V interval of patients in Group A with a good result.
† $P < 0.05$ when compared with the H-V interval of patients in Group A with a good result.
‡ $P < 0.001$ when compared with the H-V interval of all patients in Group A.
§ $P < 0.05$ when compared with the H-V interval of patients in Group A with good and fair, but not poor, results.

cant ($P < 0.01$) when the H-V interval of patients in Group A with a good hemodynamic repair was compared with that of patients with a poor result. As one might expect, the patients within the hemodynamic types of the combined Groups B, C and D generally had a significantly longer H-V interval than those in Group A (Table IV).

Prognosis: Survival in this study was not directly related to conduction disturbances. Fifty-six of the 59 patients (35 male and 21 female subjects) are alive 18 months to 16 years after operation. One patient (Case 8) died at reoperation for a residual ventricular septal defect and pulmonary stenosis. A second patient, from Group A, died at reoperation for pulmonary arterial thrombosis and pulmonary arterial hypertension. The third death occurred 9 years after initial repair (poor result) and 11 months after reoperation in a patient (Case 6) with catheterization-proved myocardial damage. Thus, there were no sudden unexplained deaths directly attributable to arrhythmia. However, two of these three patients had a markedly prolonged H-V interval.

Discussion

Our data confirm previous observations[8,9] that the His bundle interval is generally normal in patients who have few or no electrocardiographic abnormalities after intracardiac repair of tetralogy of Fallot. In contrast, as many of 60 percent of patients with electrocardiographic patterns of bifascicular block (Group B), trifascicular block (Group C), transient complete heart block (Group D) or transient bifascicular block (Other) had a prolonged H-V interval.

Surface electrocardiogram versus His bundle electrogram as detector of site of conduction system injury: Trifascicular block may be difficult to diagnose from the surface electrocardiogram. Prolongation of the P-R interval, an integral part of the electrocardiographic diagnosis of trifascicular block, may arise from either a prolonged A-H interval (A-V nodal or supra-His bundle delay), a prolonged H-V interval (infra-His or His-Purkinje system delay) or both. A-H delay alone was present in one (Case 9) of our five patients with trifascicular block, solitary H-V delay in one (Case 8) and delay in both A-H and H-V conduction in the remaining three. Thus the electrocardiogram does not accurately locate the site of injury in this group of patients. Patients with transient complete heart block (Group D) often manifest only right bundle branch block in the surface electrocardiogram in the presence of a prolonged H-V interval (three of our four patients). This discrepancy suggests the presence of undetected injury to the His-Purkinje system and illustrates the unreliability of the electrocardiogram as an indicator of the specific site and degree of injury within the specialized conduction tissue.

Previous studies on postoperative conduction system injury: Godman et al.,[8] reporting on His bundle electrographic findings in 17 patients with normal sinus rhythm after repair of ventricular septal defect or tetralogy of Fallot, found H-V prolongation in 5 of 10 patients with bifascicular block; all 5 had transient complete heart block. Six patients with right bundle branch block had a normal H-V interval. Our experience disclosed a similar incidence of H-V prolongation in patients with postoperative bifascicular block (2 of 5), but none of our patients had transient complete heart block (as defined in our study). Finally, three of our four patients with transient complete heart block had a prolonged H-V interval, thus suggesting that transient complete heart block may be a better indicator of late postoperative impairment of A-V conduction than isolated bifascicular block. Pahlajani et al.[9] reported abnormal conduction within the A-V node and His-Purkinje system in 7 of 18 patients with bifascicular block with repair of ventricular septal defect or tetralogy of Fallot; 4 patients had H-V prolongation. Thus, although all 18 of their patients were clinically well, almost 40 percent with postoperative bifascicular block had abnormalities within the specialized conduction tissue; in comparison, 60 percent (9 of 15) of our patients with abnormal postoperative electrocardiograms (Groups B, C and D) had a prolonged H-V interval.

The origin of the conduction abnormalities is not fully known but is probably a result of direct surgical injury to the His bundle or A-V node.[25–28] The surface electrocardiogram may not be helpful in locating the site of this injury.[11,15,29,30] The pattern of bifascicular block (right bundle branch block and left anterior hemiblock) has been interpreted to mean injury to both the left anterior division of the left bundle branch and the right bundle branch.[31] However, similar patterns have been produced in both canine and human hearts with (1) right ventriculotomy in conjunction with injury to the

left anterior division of the left bundle branch, (2) disruption of fibers within the proximal common bundle of His, or (3) injury to the right bundle branch and left anterior division of the left bundle branch.[28–35]

Godman et al.,[8] relating the site of surgical heart block to the surface electrocardiogram, demonstrated infra-His (within the distal His-Purkinje system) complete heart block in four postoperative patients who manifested bifascicular block in the electrocardiogram preceding the onset of complete heart block; in one postoperative patient with evidence of only right bundle branch block in the electrocardiogram before the onset of complete heart block, His bundle recordings revealed supra-His block (within the A-V node). In contrast, Anderson et al.[36] were unable to predict the site of conduction abnormality from the electrocardiogram. They reported on two patients with repair of tetralogy of Fallot who had postoperative transient complete heart block; after resumption of A-V conduction, His bundle studies disclosed a supra-His (within the A-V node) conduction disturbance in one patient and an infra-His (within the distal His-Purkinje system) conduction disturbance in the other. In addition, atrial pacing studies resulted in maintenance of 1:1 conduction to a paced rate of 180 beats/min in the patient with supra-His delay (similar to our Patient 9) and a Wenckebach (Mobitz type I) phenomenon in the His-Purkinje system of the patient with infra-His delay (similar to our Patient 14). Thus, neither the site nor the degree of postoperative injury to the conduction system may be evident in the surface electrocardiogram[37]; indeed, as illustrated by the second case of Anderson et al.,[36] the data of Pahlajani et al.[9] and our Patients 9 and 14, functional abnormalities in A-V conduction may become manifest only with use of the extrastimulus technique or atrial pacing.

Types of postoperative bifascicular block: In view of these clinical and experimental observations, two types of postoperative bifascicular block have been postulated.[11] One type results from disruption of the left anterior division of the left bundle branch (left anterior hemiblock) and injury to the peripheral right ventricular Purkinje network. The right bundle and posterior division of the left bundle remain intact; thus, true bifascicular block is not present despite the electrocardiographic pattern. A second type of bifascicular block is the result of damage to two fascicles, the left anterior division of the left bundle branch and the right bundle branch. Furthermore, damage to the right bundle branch and left anterior division resulting in a pattern of bifascicular block in the surface electrocardiogram may be caused by a single selective lesion within the proximal common His bundle. The difference between these two postulated types of bifascicular block may account for the reported difference in prognosis for patients with bifascicular block after repair of tetralogy of Fallot. Measurement of the activation time of the right ventricular apex, as an estimate of one integrity of the right bundle branch, may prove useful in distinguishing true right bundle branch block from interruption of the Purkinje network.[38,39]

Our data suggest that the surgical technique during the intracardiac repair is related to the degree of injury to the specialized conduction system. There was a significant difference in H-V interval between patients operated on before and after 1970 that was not related to age at operation or hemodynamic result. This observation suggests that technologic development and increasing surgical awareness of the importance of the underlying conduction tissue probably played a role in the observed variation in H-V intervals and may account for the reported variable experience with bifascicular block.

Relation of H-V prolongation to surgical result and prognosis: Although no data are available with regard to the long-term prognosis of patients with bifascicular block with H-V prolongation after repair of tetralogy of Fallot, increased mortality[40–43] and depressed myocardial function[44] have been reported in adult patients with ischemic heart disease and these conduction disturbances. Our data relating hemodynamic outcome to electrocardiographic groups (Table III) and to H-V intervals (Table IV) show an association between hemodynamic results and findings in the electrocardiogram and His bundle electrogram. Although there was a wide range of H-V intervals, especially in Groups B, C and D, the state of the His-Purkinje system tended to be directly related to the adequacy of the hemodynamic repair. Thus, the poorer the hemodynamic result the more likely one is to encounter a prolonged H-V interval. Furthermore, the likelihood and magnitude of the H-V prolongation increases when the surface electrocardiogram discloses a conduction disturbance, as in our Groups B, C and D.

Progression to complete heart block in adults with chronic bifascicular block, especially with H-V prolongation, appears to be related in part to the duration of bifascicular block.[45] Therefore, in children who undergo repair of tetralogy of Fallot early in life, it is important not only to achieve a good hemodynamic result, but also to preserve normal A-V conduction. In this regard, the five patients in our Group A who were operated on before age 2 years had a normal H-V interval; four of these had a good hemodynamic result.

Therapeutic implications: His bundle electrograms are useful in detecting and localizing the site of injury to the A-V conduction system, and should be obtained in patients with repair of tetralogy of Fallot, particularly when bifascicular block, trifascicular block or transient complete heart block develops. Our experience with the patients in Group A in whom good hemodynamic results of repair were associated with an intact A-V conduction system, particularly in children less than 2 years of age, supports the concept of early surgical repair. Patients who sustain specialized A-V conduction injury at operation (Groups B, C and D) warrant close follow-up for signs of deterioration in A-V conduction. Present follow-up data are not sufficient to permit prediction of progression of these various A-V conduction abnormalities or recommendations regarding their management. We reserve the use of permanent pacemakers for patients with permanent complete heart block. In addition, patients who manifest both H-V prolongation in the His bundle electrogram and symptomatic ventricular arrhythmias may be candidates for a permanent (demand) pacemaker for either overdrive suppression or vigorous antiarrhythmic therapy. When adequate long-term clinical and electrophysiologic follow-up studies become available, information regarding both prognosis and prophylactic pacemaker therapy may emerge.

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Wolff-Parkinson-White Syndrome in the Neonate

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Of 16 infants who presented with paroxysmal supraventricular tachycardia in the neonatal period, 50 percent had an electrocardiographic pattern consistent with Wolff-Parkinson-White conduction, type A. It is suggested that infants have bypass pathways similar to or identical with a Kent pathway as part of normal maturation. Infants with paroxysmal supraventricular tachycardia have electrically active bypass tracts but these are documented in only about one half of the patients because of the short duration of recordings or because of concealment (the bypass tract conducts only in retrograde fashion). The activity of these pathways is enhanced by the predominant cholinergic innervation of the neonatal heart. Resolution of the arrhythmias and the Wolff-Parkinson-White pattern in most patients occurs because of anatomic maturation of the conduction tissue, development of adrenergic innervation and a decrease in cholinergic dominance. In some children, maturation is incomplete and the bypass fibers remain quiescent or become active under certain circumstances such as those associated with increased autonomic discharge. Extended surveillance is recommended for all infants who present with paroxysmal supraventricular tachycardia and the Wolff-Parkinson-White pattern.

The incidence rate of the Wolff-Parkinson-White pattern in paroxysmal supraventricular tachycardia in infants and children has been reported to be as low as 13 percent[1,2] and as high as 51 percent.[3] This wide variation may correlate with the frequency and duration of electrocardiographic recordings. It is probable that the association is even higher because the preexcitation pattern may be transient[3–7] or concealed.[8] In fact, anterograde conduction through the bypass pathway may be so fleeting that it appears and disappears within the same recording of a standard electrocardiogram. This is especially true in the neonate.

This report describes 16 infants without gross anatomic heart disease who were treated for paroxysmal supraventricular tachycardia in the neonatal period. Eight of these infants exhibited the Wolff-Parkinson-White pattern, which disappeared in five and persisted in three.

Our purpose is threefold: (1) to call attention to the frequent association of the Wolff-Parkinson-White pattern in paroxysmal supraventricular tachycardia in the neonate; (2) to report the transitory nature of this pattern; and (3) to discuss the anatomic and physiologic causes of this transitoriness.

Material and Methods

The study was limited to infants presenting with paroxysmal supraventricular tachycardia in the first 30 days of life. Excluded were infants with gross anatomic heart disease. The infants were judged to be free of heart disease on the basis of physical examination, chest X-ray films and electrocardiograms taken during sinus rhythm. Sixteen neonates satisfied the criteria. In 8 of the 16, the Wolff-

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Parkinson-White electrocardiographic pattern was documented with continuous monitoring or multiple electrocardiographic recordings.

Results

Of the 16 neonates presenting with paroxysmal supraventricular tachycardia, 9 were male and 7 female. In the group with the Wolff-Parkinson-White pattern there was a male to female ratio of 5:3 (Group I, Table IA); in the group without this pattern there was a male to female ratio of 4:4 (Group II, Table IB). All patients with the Wolff-Parkinson-White syndrome manifested the type A pattern according to the classification of Rosenbaum et al.[9] There were two postmature infants in the group with the Wolff-Parkinson-White pattern and two premature infants and one postmature infant in the group without this pattern.

Group I: During a follow-up period of 1.9 to 7.2 years (mean 3.7 years), a transient Wolff-Parkinson-White pattern was observed in five of the eight infants (Table 1A). In Patient 1 (Fig. 1), the pattern appeared and disappeared in the same recording and was not observed again over a 2 year follow-up period. In the other four, the pattern was no longer apparent in recordings taken 7 days to 8 months after the initial manifestation of preexcitation. Four of the five patients have been asymptomatic without medication for 0.5 to 4.3 years. Patient 4 manifested recurrent supraventricular

TABLE I

Summary of Data on 16 Infants With Supraventricular Tachycardia With and Without Wolff-Parkinson-White Pattern

Case no.	Sex & Gestational Age	Date of Presentation	Date First WPW Recording	Disappearance of WPW Pattern	Treatment	Follow-up
			A. Group I: Infants With Wolff-Parkinson-White Pattern			
1	M, Term	8/3/74	8/20/74	8/20/74	Digoxin	2 years. Asymptomatic without digoxin for 0.5 years
2	M, Postmature	9/19/74	9/19/74	11/4/74	Digoxin, propranolol	1.9 years (1 recurrence of PSVT during medication); asymptomatic without medication for 0.5 year
3	M, Postmature	4/4/70	4/4/70	7/7/70	Digoxin	6.3 years. Asymptomatic without digoxin for 4.3 years
4	F, Term	6/2/69	6/3/69	6/10/69	Digoxin, quinidine	7.2 years. Medications stopped after 3 years; digoxin restarted 3 years later because of recurrence of PSVT; WPW pattern absent
5	M, Term	3/4/74	3/5/74	11/6/74	Digoxin	2.4 years. Asymptomatic with digoxin
6	M, Term	10/29/68	10/31/68	Pattern persists	Digoxin	2 years. Asymptomatic with digoxin for 2 years
7	F, Term	5/27/71	5/28/71	Pattern persists	Digoxin	4.8 years. Asymptomatic without digoxin for 3.2 years
8	F, Term	7/10/73	7/10/73	Pattern persists	Cardioversion, digoxin	3.1 years. Asymptomatic with digoxin
			B. Group II: Infants Without Wolff-Parkinson-White Pattern			
1	M, Postmature, large for gestational age	...	...	...	Digoxin	0.8 year. Asymptomatic with digoxin
2	F, Term	...	...	...	Digoxin	0.5 year. Asymptomatic with digoxin
3	M, Term	...	...	...	Digoxin, propranolol	3 years. Tachycardia recurred when medication stopped; asymptomatic with medication
4	M, Premature (36 weeks)	...	...	...	Digoxin	1.2 years. Asymptomatic with digoxin
5	F, Term				Digoxin	7.2 years. Without medication for 4.8 years; asymptomatic
6	M, Premature (38 weeks)	...	...	...	Procainamide for 5 months, digoxin for 3 years	6.5 years. Without medication for 4 years; asymptomatic
7	F, Term	...	...	...	Digoxin	9.8 years. Without digoxin 7.8 years; asymptomatic
8	F, Term	...	...	...	Cardioversion, digoxin	4.6 years. Without digoxin for 2.8 years; asymptomatic

PSVT = paroxysmal supraventricular tachycardia.

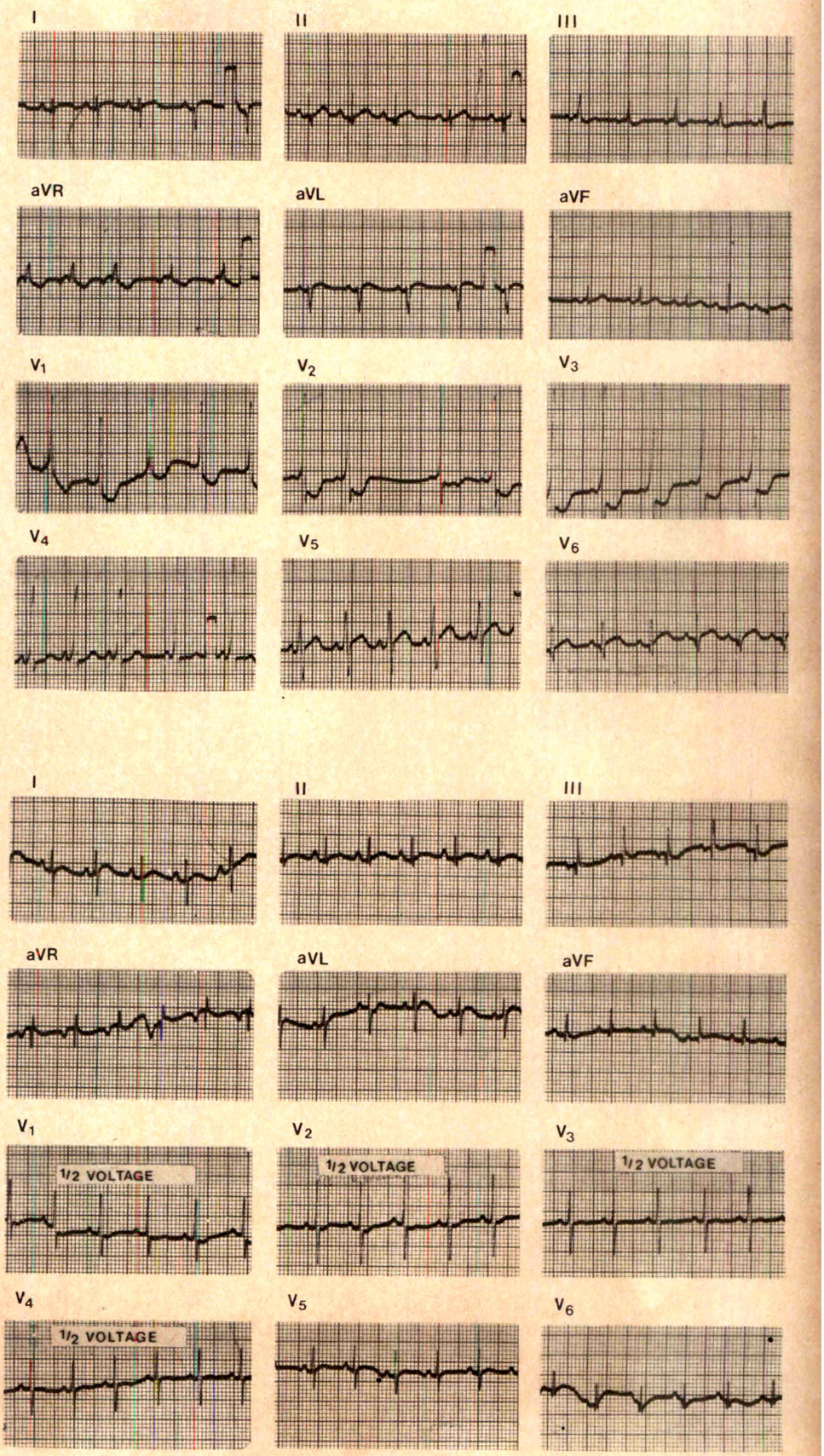

FIGURE 1. Patient 1, Group I (Table IA). **Top,** electrocardiogram showing intermittent preexcitation. The P-R interval is 0.13 second in the complexes without preexcitation and 0.07 second in the complexes with preexcitation. In lead aVF (F), beats 1, 2 and 3 demonstrate preexcitation; beats 4 and 5 are normal. The short P-R interval and delta wave are well seen in leads V_1 to V_3. **Bottom,** electrocardiogram showing a constant pattern. Preexcitation has not reappeared in 2 years of observation.

tachycardia without the Wolff-Parkinson-White pattern after being asymptomatic for 3 years. The Wolff-Parkinson-White pattern persists in Patients 6, 7 and 8. Patient 6, who was asymptomatic on digoxin therapy for 2 years, was lost to follow-up. Patient 7 has been asymptomatic without digoxin for 3.2 years, and Patient 8 has been asymptomatic for 3.1 years, but is taking digoxin.

Group II: During a follow-up period of 0.5 to 9.8 years (mean 4.2) four patients (Cases 1 to 4) have been asymptomatic with medication for 0.5 to 3 years (Table IB). Patient 3 had recurrence of tachycardia when medication was discontinued. This patient has a persistent short P-R interval and normal ventricular depolarization, a preexcitation pattern consistent with the Lown-Ganong-Levine type. In the other four patients (Cases 5 to 8) tachycardia has not recurred in a treatment-free period of 2.8 to 7.8 years.

Discussion

The prevalence of paroxysmal supraventricular tachycardia with the Wolff-Parkinson-White pattern in the neonate may result from the uniqueness of the newborn heart in reference to autonomic control and anatomic immaturity. The predominance of the newborn cholinergic system is attested to by the significant bradycardia and arrhythmias produced by clinical vagal stimulation.[10–12] A decrease in the severity and frequency of arrhythmias is noted with maturation.[12]

Autonomic control in the neonate: The autonomic sensitivity of the immature infant in utero has been studied by observing variations in fetal heart rate.[13] Severe slowing was demonstrated in a large percent of infants at all gestational ages of more than 16 weeks, but precipitous decreases in rate were less frequent as gestational age progressed beyond 29 weeks. James[14] indicated that the autonomic innervation of the human heart is primarily cholinergic in the early stages of cardiac development and that adrenergic innervation appears later and is incomplete until several months postnatally. In addition, biochemical studies[15,16] support this concept with the demonstration of diminished levels of norepinephrine in the newborn heart of other species.

Anatomy of conduction system in neonate: The newborn heart differs from the adult heart not only in autonomic influences but also in anatomy of the conduction system.[17] It has been suggested that the molding of the atrioventricular node and bundle produces pockets of tissue that may provide an altered electrophysiologic milieu that encourages the development of ectopy and reentrant rhythms.[18] Completion of the molding process with maturation may contribute to the frequent spontaneous resolution of tachycardias. Anderson[19] and Truex[20] and their co-workers have demonstrated pockets of muscular bridges between the atrium and the ventricle in the normal fetal and newborn heart. These bridges may extend from the atrium to the ventricular free wall or to the interventricular septum by means of "defects" in the anulus fibrosis. Truex et al.[20] indicated that these accessory fibers were not found in the heart of infants older than 6 months. Persistence of these bridges has been correlated with the Wolff-Parkinson-White syndrome,[21–23] and electrophysiologic studies of ventricular activation sequences[24–26] have documented that these connections may occur anywhere throughout the circumference of the anulus fibrosis.

Basis for supraventricular tachycardia and Wolff-Parkinson-White pattern in infants: We propose that anatomic incompleteness of the anulus fibrosis combined with excessive cholinergic influence accounts for the prevalence of paroxysmal supraventricular tachycardia and the Wolff-Parkinson-White pattern in the young infant. With maturation, the anulus completes itself, cholinergic influence diminishes and there is concomitant diminution in paroxysmal supraventricular tachycardia and the preexcitation pattern. It is conceivable that all infants with paroxysmal supraventricular tachycardia have some form of bypass fibers.

The infrequency of recurrence of paroxysmal supraventricular tachycardia after 1 year of age[1,2] and the disappearance of the Wolff-Parkinson-White pattern in a significant percent of patients[3–7] suggests that the normal maturation of the conduction system has occurred or that the bypass fibers exist anatomically but are electrically quiescent. The former situation probably occurs in most children, but it is clear that the latter occurs in others. Lundberg[4] reported that the Wolff-Parkinson-White pattern appeared for the first time in the late follow-up of 2 of 47 patients who had presented earlier with paroxysmal supraventricular tachycardia. Certain situations such as myocardial infarction may unveil previously quiescent bypass tracts as a result of excessive autonomic discharge associated with the infarction.[27] Enhancement of bypass conduction by cholinergic stimulation was noted in the original account of Wolff, Parkinson and White.[28]

One may implicate cholinergic activity as a predisposing factor to the increased prevalence of Wolff-Parkinson-White syndrome in the newborn in whom it is combined with an immature conduction system. Additionally, this cholinergic effect is more pronounced because of the relative adrenergic deficiency of the neonatal heart.

Prognostic implications: We believe that all infants who present with paroxysmal supraventricular tachycardia should have long term follow-up studies. Those who present with paroxysmal supraventricular tachycardia and the Wolff-Parkinson-White pattern probably warrant prolonged observation because they have a greater propensity for the development of tachyarrhythmias[2,4,29] during infancy and childhood. Nevertheless, it has been reported[7] that the prognosis is favorable for the majority of pediatric patients with the Wolff-Parkinson-White syndrome who do not have coexisting structural heart disease.

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Hemodynamics of Postmyocardial Revascularization Hypertension

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The evolution of hemodynamic variables during the development of postcoronary bypass hypertension was investigated with use of serial cardiac output determination (indocyanine green dye) in 17 patients. Seven of the 17 patients remained normotensive (Group I) during the follow-up period of 4 to 6 hours after operation, whereas 10 (Group II) had a steady increase in blood pressure (173/101 mm Hg ± 5.9/2.4 [mean ± standard error] from 132/78 ± 4.0/2.5 mm Hg immediately postoperatively, $P < 0.001$) during the same time interval. Patients in Group I had no significant change in cardiac output, total peripheral resistance or heart rate. In contrast, patients who became hypertensive had a significant increase in total peripheral resistance (47 ± 2.9 units/m^2 from an initial level of 38 ± 2.5 units/m^2, $P < 0.001$) with no significant change in cardiac index (2.73 ± 0.17 versus 2.66 ± 0.25 liters/min per m^2, $P > 0.10$). Their heart rate, which was rapid initially (102 ± 3.7 beats/min), remained unchanged during the hypertensive episode (103 ± 3.0 beats/min). The mean rate of left ventricular ejection was not reduced by the increase in pressure and even tended to increase further in all but one patient. Central venous pressure (measured in all patients) and left atrial pressure (measured in eight patients) remained constant throughout the study in both Groups I and II. The results suggest that the mechanism underlying this type of hypertension is a generalized hemodynamic disturbance possibly related to overall sympathetic overdrive rather than the result of improved cardiac performance induced by myocardial revascularization.

Since its initial description in 1973,[1] the occurrence of hypertension after myocardial revascularization has been increasingly recognized.[2,3] Its seriousness during the early period after open heart surgery has been underlined by the complications reported when its course was unchecked; these included fatal hemorrhages, cardiac decompensation and arrhythmias.[1,4,5] Because therapy to date has been mainly empirically based,[1–3] we undertook this study of the hemodynamic characteristics of the increase in pressure in the hope that it would help to define a rational approach to treatment and possibly lead to the development of preventive measures. Hypertension dependent on an increase in cardiac output would obviously require different therapeutic measures from those required by hypertension due to an increase in peripheral resistance.

Investigation of the hemodynamic basis of postoperative hypertension presents special problems. We believe that the many variables associated with myocardial revascularization preclude a valid comparison of pre- and postoperative hemodynamic indexes. Further, it is difficult to evaluate conclusions based on a comparison of indexes obtained from a single postoperative determination of cardiac output in two groups of patients, one normotensive and the other hypertensive.[3] Because the

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postoperative variability of hemodynamic functions in either group is not known, this method could not allow an adequate description of the hemodynamic evolution associated with the increase in arterial pressure. A better approach would be the serial determination of hemodynamic variations in a number of patients during the postoperative period, with each one serving as his own control. Thus, changes occurring in those who manifest hypertension could be evaluated against the background obtained from the follow-up of patients who remained normotensive.

Material and Methods

Patients: Seventeen consecutive unselected patients, 2 women and 15 men, were studied after coronary bypass surgery. The procedures involved in coronary bypass operations were clearly explained in detail during preoperative sessions in which the patients were also told of the need for routine continuous monitoring of blood pressures, central venous pressure and, sometimes, left atrial pressure. The hemodynamic studies described did not necessitate additional invasive procedures; use was made of the catheters already in place. However, the patients were told preoperatively that cardiac output determination might be performed; the technique was explained and all gave their consent. The protocol was accepted by the Institutional Review Committee. All patients were known to be normotensive preoperatively and none had evidence of significant reduction in ventricular function in the history or on clinical and radiologic examination. Their ages ranged from 33 to 65 years. In all patients, coronary artery disease had been recognized clinically from 2 weeks to 10 years before operation and confirmed preoperatively with coronary arteriography. Left ventricular end-diastolic pressure measured before ventriculography averaged 15.5 mm Hg (range 6 to 32). Left ventricular function as assessed from the left ventriculogram was judged normal in eight patients; although four of these eight had evidence of limited areas of dyskinesia in the inferior, apical or anteroapical areas of the left ventricle, overall ventricular function did not appear to be impaired. Mild to moderate overall reduction in ventricular function was reported in another eight patients; only one patient had severe impairment of myocardial contractility with areas of aneurysmal formation and increased systolic and end-diastolic volumes. Coronary arterial lesions were bypassed using either saphenous vein grafts or left internal mammary arterial anastomosis.

Surgical protocol: The anesthetic technique, agents used and postoperative management, identical in all patients, have previously been described in detail.[1,6] Anesthesia was induced with sodium pentothal (0.3 mg/kg body weight) and pancuronium bromide (0.01 mg/kg) and maintained with use of 50 percent oxygen and 50 percent nitrous oxide and analgesic concentration of either halothane (1 percent) or methoxyflurane (0.5 percent). The heart was stopped by anoxic arrest and the circulation was maintained with use of cardiopulmonary bypass, keeping a systemic flow of approximately 2.5 liters/min per m^2 body surface area to maintain a mean arterial blood pressure during perfusion of 65 to 100 mm Hg. Recovery was achieved without difficulty in all patients. A previous study showed no difference in incidence of postoperative hypertension between patients who received halothane and those given methoxyflurane.[1] Vasopressor agents or corticosteroids, or both, are not routinely used in the intra- or postoperative care of patients after coronary bypass surgery at the Cleveland Clinic. No patient included in our study had received such medications.

TABLE I

Course of Arterial Blood Pressure (mm Hg)

Case no.	Preoperative	Early Postoperative		On Discharge
		Immediate	4 Hours*	
	Group I (Normotensive After Bypass Surgery)			
1	126/88	120/80	97/64	116/74
2	114/70	117/66	101/53	110/80
3	122/78	119/66	129/71	118/70
4	130/90	104/64	103/61	127/78
5	120/78	114/65	109/54	121/70
6	112/75	115/77	115/72	117/76
7	123/77	110/55	117/60	113/76
	Group II (Hypertensive After Bypass Surgery)			
8	128/69	125/70	200/100	130/85
9	100/70	138/82	190/113	108/65
10	93/57	148/83	185/105	134/76
11	112/73	142/85	185/100	130/80
12	120/79	137/80	185/110	126/82
13	106/66	108/63	158/95	120/71
14	140/80	130/85	150/105	130/80
15	117/77	135/85	153/103	121/70
16	105/68	114/70	150/90	115/69
17	98/68	140/75	175/90	116/74

* Blood pressure recorded at time of second cardiac output (4 to 6 hours after recovery in patients remaining normotensive or during hypertensive episode in patients with a persistent increase in pressure despite adequate sedation) (see text).

After return to the recovery room, the patients were kept sedated and adequately ventilated; both arterial and central venous pressures were continuously monitored. Arterial blood gases and pH, as well as serum electrolytes and hematocrit were measured within the first 30 minutes after admission to the recovery room and every 6 hours thereafter. Any abnormality was corrected specifically as early as detected. All patients were artificially ventilated for the first 24 hours after operation to maintain arterial partial pressure of oxygen above 150 mm Hg and arterial partial pressure of carbon dioxide between 30 and 35 mm Hg. Blood losses were estimated visually and were replaced as indicated by the patient's general condition as well as by changes in arterial and central venous pressure and in left atrial pressure when the latter measurement was available; blood volume was not measured because of the controversies about its determination in the presence of unavoidable blood loss caused by the use of chest tubes, drains and other instrumentation.[7,8]

Monitoring of blood pressure: Intraarterial blood pressure was continuously monitored for the first 24 hours with use of a radial arterial cannula. Then the cannula was usually removed and the blood pressure levels were assessed thereafter by auscultation. In all patients central venous pressure was measured every 15 minutes from a catheter introduced through the internal jugular vein into the superior vena cava or right atrium. Left atrial pressure was determined in only eight patients who at operation had a catheter inserted into the left atrium at its junction with the superior pulmonary vein. Both venous catheters were left in place for 24 to 48 hours.

A hypertensive episode was defined as a sustained rise above preoperative blood pressure levels by at least 20 mm Hg for the diastolic and 30 to 40 mm Hg for the systolic level, provided that (1) this rise was not reversed with simple

TABLE II

Initial Hemodynamic Data (mean ± 1 standard error)*

	Group I (no. = 7)	Group II (no. = 10)	*P*
SBP (mm Hg)	114 ± 2.1	132 ± 4.0	<0.005
DBP (mm Hg)	68 ± 3.2	78 ± 2.5	<0.025
HR (beats/min)	92 ± 3.6	102 ± 3.7	NS
CI (liters/min per m^2)	2.13 ± 1.9	2.66 ± 0.3	NS
SI (ml/m^2)	23 ± 1.9	26 ± 2.8	NS
TPR (units/m^2)	41 ± 3.3	38 ± 2.5	NS

* Hemodynamic data obtained immediately after surgery in 17 patients, 7 who remained normotensive throughout the follow-up period (4 to 6 hours) (Group I) and 10 who had persistent hypertension during that period (Group II). CI = cardiac index; DBP = diastolic blood pressure; HR = heart rate; NS = not significant; *P* = probability; SBP = systolic blood pressure; SI = stroke index; TPR = total peripheral resistance.

sedation, and (2) there was no evidence of hypoxia, hypercarbia, shivering, fighting the ventilator or intolerance of the endotracheal tube. Thus the only hypertensive episodes studied were instances in which a high blood pressure level was maintained for at least 10 to 20 minutes in spite of proper sedation (Table I). Sedatives consisted of Pantopon® (0.03 mg/kg) given when the patient first showed signs of wakefulness and discomfort; all received this first dose. If symptoms recurred, a second dose was given, 0.015 mg/kg if needed within 2 1/2 hours of the first dose or 0.03 mg/kg if needed after that.

Hemodynamic investigation: After a 30 minute postoperative stabilization period, cardiac output was determined in every patient using indocyanine green. Continuous recording of arterial pressure resulted in a natural separation of the patients into two groups: 7 patients who remained normotensive throughout (Group I) and 10 patients who manifested hypertension during the same follow-up period (1 to 2.5 hours after operation) (Group II). In Group I cardiac output was measured again 4 hours after the first determination. In Group II cardiac output was determined before the institution of antihypertensive therapy after the blood pressure persisted at its higher level for at least 10 to 20 minutes.

Cardiac output was determined in triplicate with the dye-dilution technique (indocyanine green); 1 ml of the dye solution (5 mg/ml) was flushed as a bolus injection into the superior vena cava using the catheter introduced through the internal jugular vein at operation. After each output determination, the blood withdrawn was immediately reinfused to avoid blood loss, as described in detail previously.[9] Cardiac output was calculated with the Hamilton-Stewart technique and derived variables were calculated with standard methods.[9] For determination of ejection time, arterial pressure was recorded at a paper speed of 100 mm/sec; the values reported were averaged from at least 5 to 10 beats.

Tests of statistical significance were calculated using standard methods[10]; because each patient served as his own control, a paired *t* test was used to evaluate the hemodynamic changes associated with an increase in blood pressure. Results were considered significant when the probability (*P*) value was less than 0.01 and of questionable significance when it was less than 0.05. Values reported represent the mean ± standard error.

Results

Blood pressure course: The course of arterial pressure in the two groups of patients is summarized in Table I; the hypertensive episode was a well defined persistent rise in blood pressure as described; no patient had a recurrence of hypertension after it was controlled with nitroprusside. The two groups of patients differed initially in only one of the clinical and hemodynamic characteristics investigated: Although blood pressures in both groups were well within the normotensive range immediately after operation (114/68 ± 2.1/3.2 mm Hg in Group I and 132/78 ± 4.0/2.5 mm Hg in Group II), the latter values were significantly higher than the former (Table II).

Hemodynamic studies: The two groups differed primarily in the evolution of their hemodynamic patterns over the succeeding hours. Repeated hemodynamic studies in patients of Group I revealed a remarkable stability of values during the 4 hours of observation (Table III). The values obtained in these postoperative patients were obviously different from normal values for our laboratory[11]; the heart rate was higher (92 ± 3.6 versus 67 ± 10 beats/min), cardiac and stroke indexes were lower (2.13 ± 0.19 versus 3.1 ± 0.5 liters/min per m^2 and 23 ± 1.9 versus 45 ± 7 ml/m^2, respectively) and total peripheral resistance increased (41 ± 3.3 versus 29 ± 7 units/m^2).

The hypertensive episode in all patients of Group II was associated with a definite increase in total peripheral resistance (*P* <0.001) (Fig. 1). Despite the increase in blood pressure, the heart rate remained unchanged;

TABLE III

Follow-Up of Hemodynamic Indexes in Groups I and II

	Group I (no. = 7)			Group II (no. = 10)		
	C_1	C_2	*P**	C	HT	*P**
SBP (mm Hg)	114 ± 2.1	110 ± 2.1	NS	132 ± 4.0	173 ± 5.9	<0.001
DPB (mm Hg)	68 ± 3.2	62 ± 2.8	NS	78 ± 2.5	101 ± 2.4	<0.001
HR (beats/min)	92 ± 3.6	90 ± 1.8	NS	102 ± 3.7	103 ± 3.0	NS
CI (liters/min per m^2)	2.13 ± 0.19	2.15 ± 0.16	NS	2.66 ± 0.25	2.73 ± 0.17	NS
SI (ml.m^2)	23 ± 1.9	24 ± 2.1	NS	26 ± 2.8	27 ± 2.1	NS
TPR (units/m^2)	41 ± 3.3	38 ± 3.4	NS	38 ± 2.5	47 ± 2.9	<0.001

* Probability (*P*) values based on paired *t* test.
C = control cardiac output study; C_1 = first control cardiac output study; C_2 = second control cardiac output study (4 to 6 hours after recovery); HT = cardiac output study performed during the hypertensive episode. Other abbreviations as in Table II.

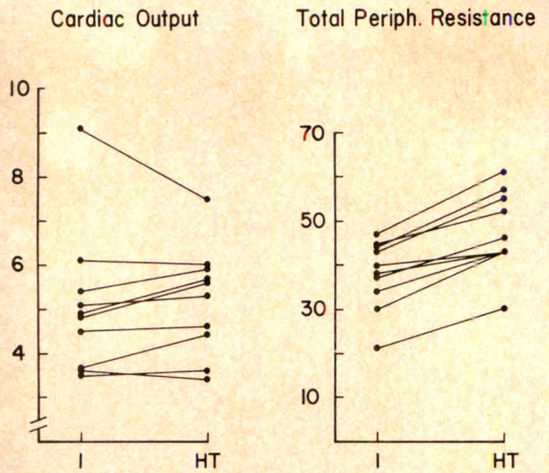

FIGURE 1. Changes in cardiac output (liters/min) and total peripheral (Periph.) resistance (units/m^2) in 10 patients who had hypertension after coronary bypass surgery. HT = hypertensive episode; I = initial study.

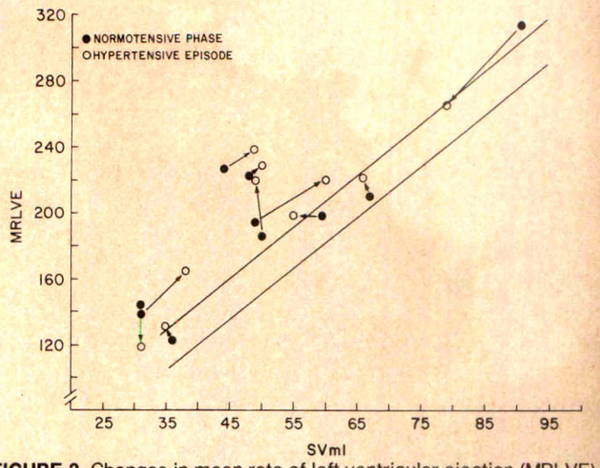

FIGURE 2. Changes in mean rate of left ventricular ejection (MRLVE) related to changes in stroke volume (SV)[12,13] during the hypertensive episode after coronary bypass surgery in 10 patients; no patient had an ejection rate depressed below normal in spite of the increase in arterial pressure. The **diagonal lines** represent the 95 percent confidence limits of the relation between mean rate of left ventricular ejection and stroke volume obtained in normal subjects.[13]

cardiac output was not significantly altered (Table III, Fig. 1).

Throughout the study, both the central venous and left atrial pressures remained within normal limits in all patients in whom they were recorded (central venous pressure was recorded in all 17 but left atrial pressure in only 8). There was no significant increase in either pressure during the hypertensive episode. The hematocrit and hemoglobin levels were determined every 6 hours and did not vary significantly during this period ($P > 0.5$). There was no correlation between changes in hematocrit and changes in cardiac index ($r = 0.073$, $P > 0.5$).

Cardiac performance during the study was evaluated from the mean rate of left ventricular ejection; changes in this index were judged in relation to alterations in stroke volume.[12,13] In all cases, this mean rate was within or even slightly above expected normal limits during the initial study and remained so during the hypertensive episode (Fig. 2). During the period of hypertension the rate tended to be higher than in the control stage in all but one patient whose rate of ejection decreased as blood pressure increased.

Follow-up: Follow-up studies of the patients for 2 weeks to 4 months postoperatively showed that none had postoperative myocardial infarction; only one patient had residual angina pectoris. No patient had a recurrence of hypertension after it was controlled with sodium nitroprusside for 6 to 12 hours postoperatively.

Discussion

Postoperative hypertension related to increased peripheral resistance: The results clearly demonstrate that the increase in blood pressure after coronary bypass surgery was related to an increase in total peripheral resistance. This conclusion is not based only on comparison of group averages; the change in hemodynamic pattern with the increase in pressure was identical in all patients who had a hypertensive episode. These observations are in basic agreement with the findings of Hoar et al.[3] However, the approach used in our study allowed a more precise definition of the hemodynamic evolution of this type of hypertension. The follow-up of hemodynamic variations over the same period of time in a group of identically treated patients is apt to show more clearly the contrast between the evolution of changes in patients who remain normotensive and patients who have postoperative hypertension. Further, each patient in our study served as his own control, and the initial hemodynamic determination was obtained early in the postoperative period; thus variability due to different factors was minimized.

The increase in total peripheral resistance strongly suggests that the pathophysiologic mechanism underlying this type of hypertension is a generalized hemodynamic disturbance rather than a simple increase in cardiac output resulting from a hypothetical improvement in performance after myocardial revascularization. This observation is consistent with previous data[1] on hypertension after internal mammary artery implantation. Hypertension due to an increase in cardiac output would not be expected to occur after the latter operation, which has been reported to produce a transient period of diminished ventricular performance.[14]

Role of hypervolemia: Our data do not suggest that the increase in arterial pressure after coronary surgery is related to hypervolemia induced by overtransfusion. However, this is an indirect conclusion because circulating blood volume was not measured directly. However, the following observations throw considerable

doubt on the suggestion that hypertension after myocardial revascularization is due to volume expansion. Central venous pressure remained within normal throughout our study and its course was not significantly different in patients who had hypertension and in those who did not. In addition, our attempts in some patients to control the increase in blood pressure by decreasing fluid infusion and blood transfusions were not successful even though central venous pressure was decreased by administration of 1 to 2 cm of saline solution. The hemodynamic evolution was also not suggestive of an initiating hypervolemia. Because hemodynamic indexes were closely monitored, an increase in cardiac output would probably have been detected if hypervolemia had initiated the hypertension. Conway[15] reported that expansion of blood volume in dogs was first associated with an increase in cardiac output; total peripheral resistance increased only after 3 hours. Because our patients had no increase in either central venous or left atrial pressure during the hypertension, the absence of an increase in cardiac output cannot be ascribed to myocardial decompensation.

Pattern of tachycardia and hyperkinetic circulation: Two paradoxical findings were associated with the increased arterial pressure and total peripheral resistance, namely, a lack of slowing of the initially rapid heart rate and further elevation of the mean rate of left ventricular ejection. The combination of these three features, increased total peripheral resistance, persistent tachycardia and elevated rate of ejection, suggests an increased sympathetic drive and might explain why cardiac output was not reduced by the rapid increase in blood pressure.[16] This pattern of tachycardia and hyperkinetic circulation was described in some types of hypertension and related to adrenergic stimulation.[17,18] Increased sympathetic activity and increased circulating catecholamines have been demonstrated uniformly during cardiopulmonary bypass[19,20] and have been thought to persist for some time after open heart surgery.[21] Whether our findings of high levels of heart rate, total peripheral resistance and mean rate of left ventricular ejection immediately after coronary bypass surgery are related to an increased sympathetic drive remains conjectural. However, it is not unreasonable to suppose that the latter might set the stage for hypertension in some patients and participate in its development or influence its hemodynamic characteristics.

The cause of the increase in pressure after coronary bypass surgery is difficult to define precisely. It has been suggested that cardiac or aortic pressor reflexes, or both, can lead to an unstable positive feedback situation[22–24] that may lead to severe hypertension.[24–26] Considerable evidence has been presented for the induction of potent pressor reflexes from different types of cardiac receptors that may be responsible for some clinical forms of paroxysmal hypertension.[26,27]

Therapeutic implications: The hemodynamic pattern described in our study indicates that a better control of these hypertensive episodes could be obtained by a reduction in alpha sympathetic activity rather than a reduction of cardiac output by beta adrenergic blockade. Intravenously administered propranolol was shown to increase total peripheral resistance partly in response to the reduction of cardiac output and also possibly because of unopposed alpha stimulation.[28] A vasodilator agent that would reduce total peripheral resistance without inducing a potentially harmful excessive cardiac stimulation[29] might also be particularly helpful to tide the patient over the hypertensive episode.

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Alpha and Beta Adrenergic Blockade with Orally Administered Labetalol in Hypertension

Studies on Blood Volume, Plasma Renin and Aldosterone And Catecholamine Excretion

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Patients with essential hypertension were treated for 6 weeks with the alpha and beta adrenoceptor blocking agent labetalol alone (no. = 18) or in combination with the diuretic agent chlorthalidone (no. = 11). Maximal doses of labetalol during these trials averaged 1,460 and 650 mg/day, respectively. Significant ($P < 0.05$) changes during therapy with labetalol alone included a transient decrease in supine blood pressure reaching a maximum of 11 percent, persistent reduction in upright blood pressure, pulse rate (20 percent) and plasma renin activity (40 percent), a gain of 1.7 percent in body weight and of 17 percent in blood volume, a sevenfold rise in epinephrine excretion rate and a mild increase in plasma potassium; plasma aldosterone and norepinephrine excretion rate remained unaltered. After 6 weeks of combination therapy, blood pressure reduction was greater ($P < 0.02$) than after labetalol alone in both the supine (14.4 versus 4.3 percent) and upright (18.6 versus 11.6 percent) positions; blood volume and plasma potassium were decreased ($P < 0.05$), plasma renin was doubled ($P < 0.02$) and plasma aldosterone was unchanged. Orthostatic hypotension and several other side effects were common with large doses of labetalol but infrequent at doses used during combination therapy; moreover, these effects were often transient. These data indicate that combined alpha and beta adrenoceptor blockade with labetalol may effectively reduce blood pressure in patients with essential hypertension, with a somewhat more pronounced effect in the upright position. Extracell fluid retention may reduce the sensitivity of supine blood pressure to treatment, but this effect is avoided with concomitant diuretic therapy. Labetalol's antihypertensive action appears to be renin-independent and is associated with a marked increase in epinephrine excretion.

Although combined alpha and beta adrenergic blockade has been advocated for more than a decade in the treatment of pheochromocytoma[1] and other forms of hypertension,[2] serious side effects of alpha blocking agents, particularly orthostatic hypotension,[2] have prevented wider acceptance of such treatment.

Recently, labetalol, a compound with combined alpha and beta adrenergic blocking potency in a ratio of 6:1,[3] has become available for clinical use and has been shown to reduce blood pressure by decreasing peripheral vascular resistance[4–6] in normal subjects and patients with hypertension.[4–12] This study was undertaken to evaluate labetalol in patients with essential hypertension and to investigate its effects on interrelations between blood pressure and major factors regulating it such as plasma renin activity and aldosterone levels, body fluid and electrolyte balance and catecholamine excretion rates.

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Methods

Patients: Eighteen patients with benign essential hypertension were included in the study. There were 7 women and 11 men ranging in age from 28 to 69 years. All were informed about the purpose and investigative character of the study, and all gave their consent. Secondary forms of hypertension were excluded with the usual clinical and laboratory procedures. No patient had retinal hemorrhage or exudates, papillary edema or heart failure, and all had plasma creatinine levels below 1.4 mg/100 ml. The study was conducted on an outpatient basis. The patients were instructed not to add salt to their diet for at least 1 week before the investigation.

Study protocol: The study plan included an initial placebo phase of 2 to 4 weeks' duration, followed by a treatment phase of 6 weeks and a second placebo period of 2 to 4 weeks. The patients were seen weekly for determination of body weight, blood pressure and pulse rate after 10 minutes in the supine and 2 minutes in the upright position. The following procedures were performed at the end of each placebo phase and after treatment for 2, 4 and 6 weeks: a 24 hour collection of urine was made for determination of sodium, potassium and creatinine excretion levels; the patients completed a questionnaire with 35 questions regarding the presence and severity of various symptoms commonly associated with hypertension or antihypertensive drug therapy; venous blood was obtained between 8 and 11 AM after 1 hour of quiet walking for measurement of plasma sodium, potassium and creatinine concentrations, plasma renin activity and plasma aldosterone levels; except for the second week of treatment, blood volume was determined simultaneously. In addition, supine (1 hour) plasma electrolytes, renin activity and aldosterone levels were measured and urinary catecholamine excretion rates were determined at the end of treatment and after both placebo phases. Labetalol was administered in three divided doses, starting with a total of 300 mg/day during the first week and stepwise weekly increments up to 2,000 mg or until blood pressure was decreased to less than 140/90 mm Hg or intolerable effects appeared.

After completion of the second placebo phase, 11 patients underwent a 6 week course of treatment with labetalol in combination with the diuretic drug chlorthalidone. The latter was given in a fixed dose of 100 mg daily; oral potassium supplements were added to keep plasma potassium levels above 3.2 mEq/liter. To prevent possible orthostatic hypotension, relatively small doses of labetalol (300 to 600 mg/day) were used during the initial 3 weeks; if blood pressure remained elevated (more than 140/90 mm Hg), the dose of labetalol was doubled for the second 3 week period. In this part of the study, all values measured during treatment with labetalol alone, with the exception of urinary catecholamines, were again determined at the end of the 6 weeks treatment period when blood was obtained after 1 hour of quiet walking. Body weight, blood pressure, pulse rate and plasma electrolytes were also monitored after 3 weeks of therapy.

Techniques: Blood pressure was measured with a standard cuff and sphygmomanometer, each value representing the mean of three recordings. The pressure at the disappearance of the Korotkoff sounds was taken as the diastolic pressure. Mean pressure was calculated as the sum of the diastolic and one third of the pulse pressure. Plasma and urinary sodium and potassium concentrations were estimated with an Instrumentation Laboratory flame photometer and plasma creatinine level with an autoanalyzer. Plasma renin activity and plasma aldosterone levels were measured with radioimmunoassay methods.[13,14] Blood volume was determined with an isotope-dilution technique[15] using the method of Kuni et al.[16] for chromium-51 tagging of erythrocytes and a 15 minute equilibration period. Blood volume was expressed in milliliters per kilogram of lean body mass.[17] Urinary adrenaline and noradrenaline concentrations were determined with the method of Bertler et al.[18] Statistical analysis was undertaken with standard techniques; for t tests and linear regression analysis, the natural logarithm transformation of plasma renin or aldosterone levels or catecholamine excretion rates was used. Changes during treatment with labetalol were analyzed using a paired t test.

Results

Labetalol Therapy Alone

Dosage: The maximal dose of labetalol was 300.0 ± 0 (standard error) mg in the first week of treatment and 533 ± 30 mg in the second, 722 ± 29 mg in the third, 994 ± 59 mg in the fourth, 1,277 ± 79 mg in the fifth and 1,459 ± 114 mg in the sixth week of treatment (Fig. 1).

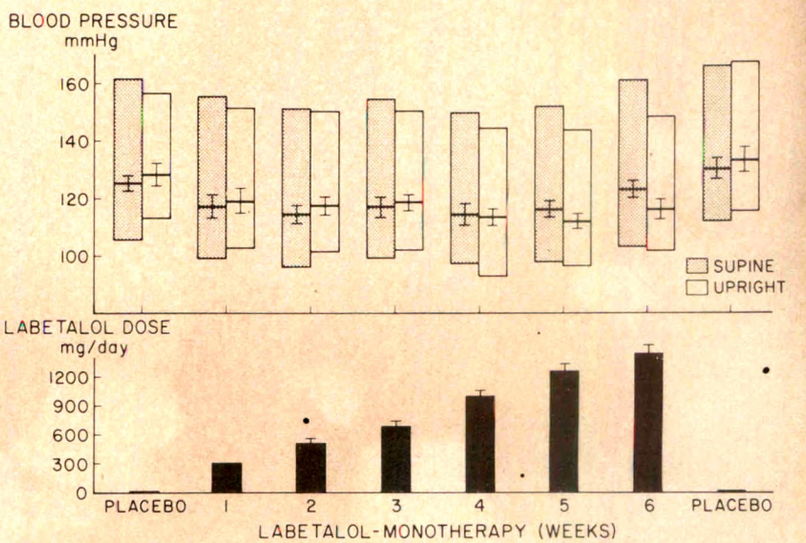

FIGURE 1. Effect of a 6 week course of treatment with labetalol alone in increasing doses **(lower panel)** on supine and upright systolic, diastolic and mean (± standard error) blood pressure **(upper panel)** in patients with essential hypertension.

TABLE I

Changes in Body Weight, Hematocrit and Plasma and Blood Volumes in 18 Patients Treated With Labetalol (mean ± standard error)

	First Placebo Phase	Labetalol		Second Placebo Phase
		4 Weeks	6 Weeks	
Body weight (kg)	78.7 ± 3.2	79.3 ± 3.2*	81.2 ± 3.3*	79.9 ± 3.3
Hematocrit (%)	46.2 ± 1.0	43.9 ± 0.9*	43.9 ± 1.0*	45.9 ± 1.0
Plasma volume (ml/kg lean body mass)	45.2 ± 1.8	47.6 ± 3.3	54.2 ± 2.2†	46.2 ± 2.2
Blood volume (ml/kg lean body mass)	78.8 ± 3.2	81.0 ± 5.4	92.2 ± 3.4*	80.8 ± 3.4

* Probability (P) <0.05 versus first placebo phase.
† P <0.005 versus first placebo phase.

Blood pressure: Average blood pressure values after the first and second placebo periods were, respectively, 161/106 ± 5/2 and 170/112 ± 5/3 mm Hg in the supine position and 157/113 ± 5/3 and 172/116 ± 7/4 mm Hg in the upright position (Fig. 1). The mean values of the two placebo periods were used for statistical comparison with blood pressure measurements during labetalol therapy and for calculation of the labetalol-induced percent changes in mean blood pressure. Supine blood pressure decreased significantly to 155/99 ± 5/3 mm Hg (−8.7 ± 1.8 percent; P <0.001) after 1 week of treatment and to 151/96 ± 5/2 mm Hg (−10.5 ± 1.9 percent; P <0.001) after 2 weeks. Despite the progressive increase in dose, there was no further decrease in supine blood pressure thereafter, and stable blood pressure reductions of 8.2 ± 2.1, 10.4 ± 2.2 and 10.1 ± 1.4 percent (P <0.005) occurred after 3, 4 and 5 weeks, respectively. Moreover, after 6 weeks of labetalol therapy the supine blood pressure increased slightly to 162/103 ± 5/2 mm Hg (−4.3 ± 2.7 percent) so that the difference from pretreatment values became insignificant (P <0.2).

The reduction in blood pressure effected with labetalol was somewhat greater in the upright than in the supine position; significant reductions were observed during the entire study period (P <0.001). Percent decreases in upright blood pressure were 9.2 ± 1.4 percent after 1 week of treatment, reached a maximum of 15.0 ± 1.2 percent after 5 weeks and were again somewhat blunted after 6 weeks of therapy (11.6 ± 1.8 percent). In contrast, the orthostatic reductions in blood pressure reached a maximum of 7 percent in the sixth week of treatment, in parallel with the labetalol dose.

Pulse rate: The mean values of the two placebo periods were used for statistical comparison with measurements during labetalol therapy and for calculation of labetalol-induced percent changes in pulse rate. During treatment with labetalol, supine pulse rate was decreased significantly (P <0.001) from 76 ± 3 to 67 ± 3 beats/min (−11.3 ± 2.2 percent) after 2 weeks, to 64 ± 2 beats/min (−14.8 ± 2.0 percent) after 4 weeks and to 60 ± 2 beats/min (−20 ± 2.2 percent) after 6 weeks; upright pulse rate decreased (P <0.001) from 87 ± 3 to 73 ± 3 beats/min (−16.0 ± 2.3 percent) after 2 weeks, to 71 ± 3 beats/min (−18.4 ± 2.2 percent) after 4 weeks and to 66 ± 3 beats/min (−24.4 ± 2.3 percent) after 6 weeks. Thus, mean percent pulse reduction in the upright position slightly exceeded that during recumbency (P <0.05).

Body fluid and electrolyte status: Plasma and blood volumes measured during placebo conditions were normal (Table I). Labetalol caused progressive significant (P <0.05) increases in plasma and blood volumes and body weight, and hemotocrit decreased by about

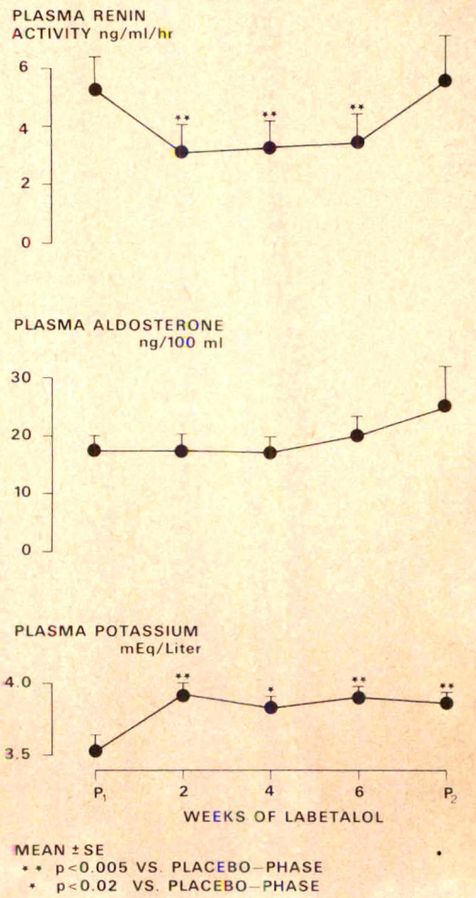

FIGURE 2. Effect of labetalol on upright plasma renin, aldosterone and potassium levels. p = probability; P_1 and P_2 = first and second placebo phase, respectively; SE = standard error.

2 percent ($P < 0.05$). Compared with the mean values from both placebo periods, mean percent increases after 4 and 6 weeks of therapy, respectively, were 11.3 ± 4.3 and 21.0 ± 5.7 percent for plasma volume, 7.1 ± 4.8 and 17.2 ± 5.7 percent for blood volume and 1.2 ± 0.4 and 1.7 ± 0.6 percent for body weight.

During placebo conditions, the mean plasma sodium level was 139.2 ± 0.5 mEq/liter, and urinary sodium and potassium excretion rates were 181 ± 21 and 65 ± 7 mEq/24 hour, respectively; there were no significant changes in these values during labetalol therapy. In contrast, plasma potassium increased significantly ($P < 0.02$) from 3.5 ± 0.1 to approximately 3.9 mEq/liter after 2 to 6 weeks of treatment and remained at 3.9 ± 0.1 after the second placebo phase (Fig. 2).

Plasma renin and aldosterone: Upright plasma renin activity decreased significantly ($P < 0.005$) from 5.2 ± 1.4 ng/ml per hour before treatment to 3.1 to 0.9 after 2 weeks of labetalol therapy, without further renin suppression between the fourth and sixth weeks of treatment. After the second placebo phase, plasma renin activity again increased to pretreatment levels (Fig. 2). Supine plasma renin also decreased during labetalol therapy (2.7 ± 0.8 versus 4.0 ± 1.1 ng/ml per hour; $P < 0.001$). Mean supine or upright plasma aldosterone concentrations (Fig. 2) did not change significantly during labetalol therapy.

Urinary catecholamines (Fig. 3): Twenty-four hour urinary norepinephrine and epinephrine excretion rates after the first placebo phase were 21.8 ± 2.5 and 4.7 ± 1.7 μg/g creatinine, respectively; these values are comparable with the excretion rates obtained from 45 normal control subjects (29.0 ± 1.9 and 3.4 ± 0.6 μg/g creatinine).[19] The excretion rate of norepinephrine was unchanged during labetalol therapy. In contrast, the excretion rate of epinephrine after 6 weeks of labetalol increased markedly to 33.6 ± 5.1 μg/g creatinine ($P < 0.001$) and returned toward pretreatment values at the end of the second placebo period. Incubation of urine with various concentrations of labetalol revealed no interference of the latter with the determination of catecholamines.

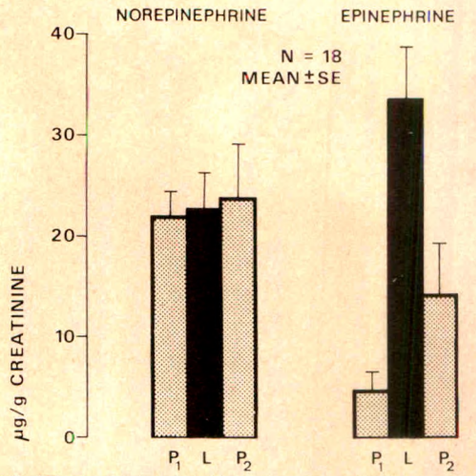

FIGURE 3. Effect of labetalol (L) alone on calecholamine excretion rates. N = number of patients. Other abbreviations as in Figure 2.

Relations between changes in blood pressure and various measurements: The labetalol-induced percent changes in supine or upright blood pressure did not correlate significantly with pretreatment values or labetalol-induced changes in plasma renin, blood volume or catecholamine excretion rates.

Side effects: Subjective symptoms associated with therapy were assessed by subtracting the presence and

TABLE II

Effects of Combined Treatment with Labetalol and Chlorthalidone

	Placebo*	Labetalol + Chlorthalidone	
		3 Weeks	6 Weeks
Drug dose (g/day)			
Labetalol	0	0.44 ± 0.05	0.65 ± 0.09
Chlorthalidone	0	0.1	0.1
Blood pressure (mm Hg)			
Supine	168/109 ± 5/3	150/99 ± 5/3†	144/93 ± 5/4†
Upright	168/116 ± 7/4	139/95 ± 5/3†	135/92 ± 5/4†
Pulse rate (beats/min)			
Supine	75 ± 4	70 ± 3	66 ± 2§
Upright	86 ± 4	79 ± 3	73 ± 3‡
Plasma potassium (mEq/liter)	3.8 ± 0.1	3.2 ± 0.1†	3.4 ± 0.1§
Body weight (kg)	81.5 ± 4.0	80.6 ± 3.9	80.8 ± 3.9
Plasma volume (ml/kg lean body mass)	45.7 ± 2.1	. . .	39.6 ± 2.2‡
Blood volume (ml/kg lean body mass)	82.0 ± 3.3	. . .	69.4 ± 3.2†
Hematocrit (%)	46.9 ± 1.7	. . .	46.1 ± 1.4
Plasma renin activity (upright) (ng/ml per hour)	4.9 ± 2.2	. . .	9.5 ± 2.2§
Plasma aldosterone (upright) (ng/100 ml)	21.1 ± 7.6	. . .	22.2 ± 5.2

* Mean values of placebo phases I and II.
† Probability (P) <0.005 versus placebo phase.
‡ $P < 0.01$.
§ $P < 0.02$ versus placebo phase.

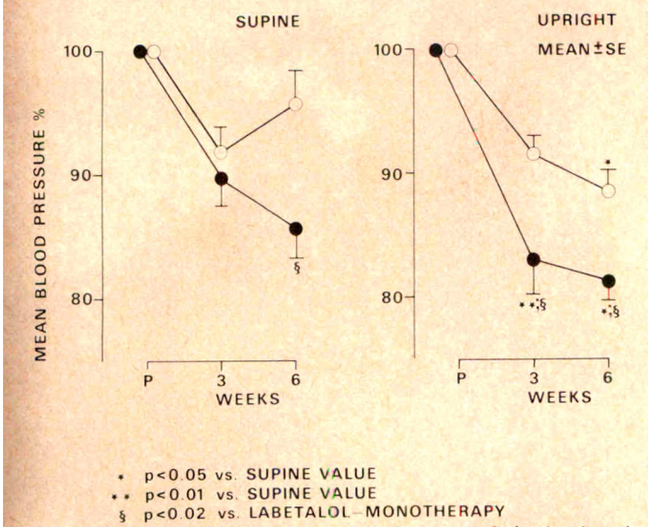

FIGURE 4. Percent changes in mean blood pressure during treatment with labetalol alone **(open circles)** or in combination with chlorthalidone **(closed circles).** P = mean value of first and second placebo phases. Other abbreviations as in Figure 2.

degree (mild, moderate, severe or intolerable) of complaints reported by the patients during the placebo phases from those described during treatment. Symptoms associated with labetalol therapy included orthostatic dizziness in six patients; dry mouth in four; tiredness, sleepiness, headache or palpitation, each in three; exertional dyspnea, nasal congestion, facial flush, diminished appetite or epigastric discomfort, each in two; and nausea, vomiting, flatulence, pruritis, cold hands and feet, vivid dreams, precardial feeling of tightness or increased loss of scalp hair, each in one patient. These symptoms were often transient and they were of only mild to moderate severity, never necessitating discontinuation of drug therapy. The occurrence of orthostatic dizziness appeared to be dose-dependent.

Combined Labetalol-Diuretic Therapy

The mean daily labetalol-dose was 436 ± 47 mg during the first 3 weeks and 655 ± 89 mg during the remaining 3 weeks of therapy; the daily dose of chlorthalidone was 100 mg (Table II). This combined therapy caused significant reductions in supine and upright blood pressure ($P < 0.005$), pulse rate ($P < 0.025$) and plasma and blood volumes ($P < 0.05$); body weight decreased only slightly whereas plasma renin increased significantly ($P < 0.02$) (Table II).

Blood pressure: Although the mean labetalol doses given during labetalol therapy alone were more than twice as large as those given during combined treatment with chlorthalidone, the antihypertensive efficiency of the latter regimen was significantly greater ($P < 0.02$) (Fig. 4). Thus, the combination therapy reduced supine and upright mean blood pressure by 10.5 ± 2.0 and 17.0 ± 2.7 percent after 3 weeks of treatment and by 14.4 ± 2.4 and 18.6 ± 6.0 percent, respectively, after 6 weeks; reductions in blood pressure were again somewhat more pronounced in the upright than in the supine position ($P < 0.05$). Moreover, with the combined therapy normal blood pressure levels were achieved in 6 of the 11 patients.

Plasma and urinary electrolytes and aldosterome levels: Despite administration of potassium supplements, plasma potassium decreased ($P < 0.02$) from a mean value of 3.8 ± 0.1 to 3.2 ± 0.1 and 3.4 ± 0.1 mEq/liter after combined treatment for 3 to 6 weeks, respectively (Table II). Plasma aldosterone, plasma sodium and creatinine levels or urinary electrolyte excretion rates were not significantly altered.

Plasma renin and blood volume: During combined labetalol-diuretic therapy, there were no significant correlations between changes in supine or upright blood pressure and pretreatment values or changes in plasma renin activity or blood volume, singly or in combination.

Side effects: These included orthostatic dizziness, facial flush, nasal congestion, dry mouth, dyspnea or impotence, each in one patient.

Discussion

In this study, patients with benign essential hypertension were treated for 6 weeks orally with the alpha-beta adrenoceptor anatagonist labetalol alone or in combination with the diuretic agent chlorthalidone. Significant ($P < 0.05$) cardiovascular, physical and endocrine changes observed during treatment with labetalol alone in doses increasing weekly included a transient decrease in supine blood pressure; persistent reductions in upright blood pressure, in pulse rate and plasma renin activity; increases in body weight and in plasma and blood volumes indicating sodium and fluid retention, and a marked rise in epinephrine excretion rate.

Extracell fluid volume expansion with labetalol: Long-term therapy with the currently available nondiuretic antihypertensive drugs without the concomitant use of a diuretic agent is usually impractical because of the insensitivity of blood pressure that develops as a result of volume retention.[20–22] Possible exceptions are the beta adrenergic blocking agents,[23,24] which usually have little influence on circulatory volume.[25,26] Certain reports[5,6,9–11,27] suggested that labetalol is an additional type of drug that, when used alone, may provide satisfactory reduction of blood pressure over periods of months to years. Although long-term follow-up observations were not made in our study, our data suggest that with labetalol therapy alone the responsiveness of supine blood pressure may diminish in the early stage of treatment and that the agent's antihypertensive efficiency is better maintained in the upright position. Thus, supine blood pressure was reduced by an average of 8.7 and 10.5 percent, respectively, as early as the first and second weeks of treatment with labetalol alone ($P < 0.001$), but this initially good response was maintained only until the fifth week of treatment despite a marked increase in dose. Thereafter, supine blood pressure tended to increase, almost

returning to the pretreatment level at the end of the sixth week. The blunting of labetalol's antihypertensive efficacy in the supine position was probably due to the concomitant extracell fluid volume expansion, the latter resulting from the alpha adrenoceptor blocking action of the drug.[28]

A somewhat greater antihypertensive effect of labetalol therapy persisting throughout the study period was observed when the patients were upright. In this position the mean reduction in blood pressure reached a maximum of 15.0 percent ($P < 0.001$) after 5 weeks and remained significant (11.6 percent; $P < 0.001$) after 6 weeks of labetalol therapy. Orthostatic decreases in blood pressure causing dizziness occurred in six patients, preventing us from increasing the dose according to the predetermined schedule. Because beta blocking agents are renowned for not causing orthostatic hypotension,[23,24] whereas administration of phenoxybenzamine may cause severe, often troublesome postural decreases in blood pressure[2] by interfering with peripheral vasoconstriction,[21] it is reasonable to assume that the observed decrease in blood pressure in the upright posture was largely due to the blocking of alpha adrenergic receptors.

Effect on cardiac and renal beta receptors: The reductions in pulse rate ($P < 0.001$) and plasma renin activity ($P < 0.005$) induced by labetalol probably reflect this drug's potent influence on cardiac and renal beta receptors.[23,24,29] Decreases in pulse rate seemed to be dose-related, and maximal reductions of 24 and 27 percent, respectively, in the supine and upright positions were observed after 6 weeks of treatment, that is, at a mean labetalol dose of 1,460 mg/day. In contrast, maximal renin inhibition averaging 40 percent occurred as early as the second week of treatment, at a relatively small mean labetalol dose of 533 mg/day; thereafter, a progressive increase in dose had no further effect on plasma renin activity. The failure of plasma aldosterone to decrease in association with the reduced plasma renin activity may have been due to a stimulating influence from a concomitant rise in plasma potassium[30,31]; the latter has also been observed during treatment with beta blocking agents.[26,33]

Effect on catecholamine excretion: The excretion rate of norepinephrine remained unchanged during labetalol therapy. The sevenfold ($P < 0.001$) increase in the excretion rate of epinephrine is probably another consequence of alpha receptor inhibition,[33–35] because catecholamine excretion was unaltered or decreased slightly after beta blockade.[26,36,37] The significance of this alteration for the hypotensive action of labetalol needs further clarification.

Combined labetalol-diuretic therapy: When given in conjunction with a diuretic drug, labetalol had a persistent antihypertensive effect in this and previous studies.[8,12] Mean reductions in blood pressure observed in our patients after 6 weeks of combination therapy were significantly ($P < 0.02$) greater than those after labetalol therapy alone in both the supine (14.4 versus 4.3 percent) and upright (18.6 versus 11.6 percent) positions. Moreover, the mean doses of labetalol given during combination therapy were much smaller than those used during treatment with labetalol alone (655 versus 1,459 mg/day). With the smaller doses the mild to moderate side effects that occurred commonly and in all patients during treatment with labetalol became infrequent during combination therapy; thus, the latter regimen was well tolerated and reduced blood pressure to normal in 6 of 11 patients. It is probable that with the use of larger doses of labetalol in combination with a diuretic drug, greater antihypertensive efficiency may be achieved. Such therapy has been found to be effective even in some patients with severe hypertension refractory to other antihypertensive drugs, although side effects, notably orthostatic hypotension, were again more prominent when these large labetalol doses were used.[38]

Relation to renin inhibition: Because it has been suggested that certain beta blocking drugs may exert their antihypertensive effect partly through renin inhibition,[32] we also evaluated labetalol in this regard. Although plasma renin activity decreased during treatment with labetalol alone, an increase was noted during combination treatment ($P < 0.02$). The latter dissociation[39] and the lack of a significant relation between renin and blood pressure during treatment with the single drug suggest that the antihypertensive mechanism of labetalol is renin-independent.

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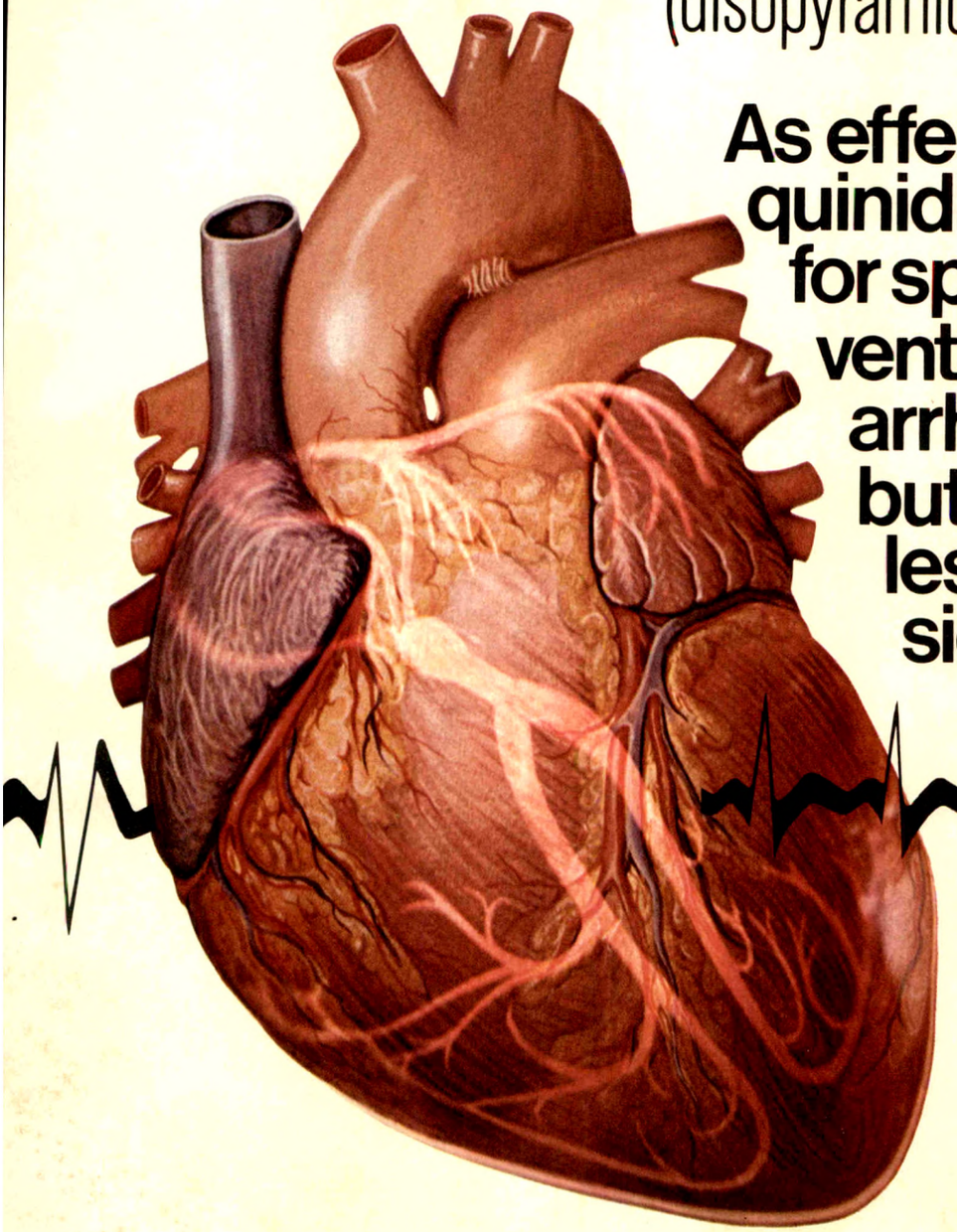

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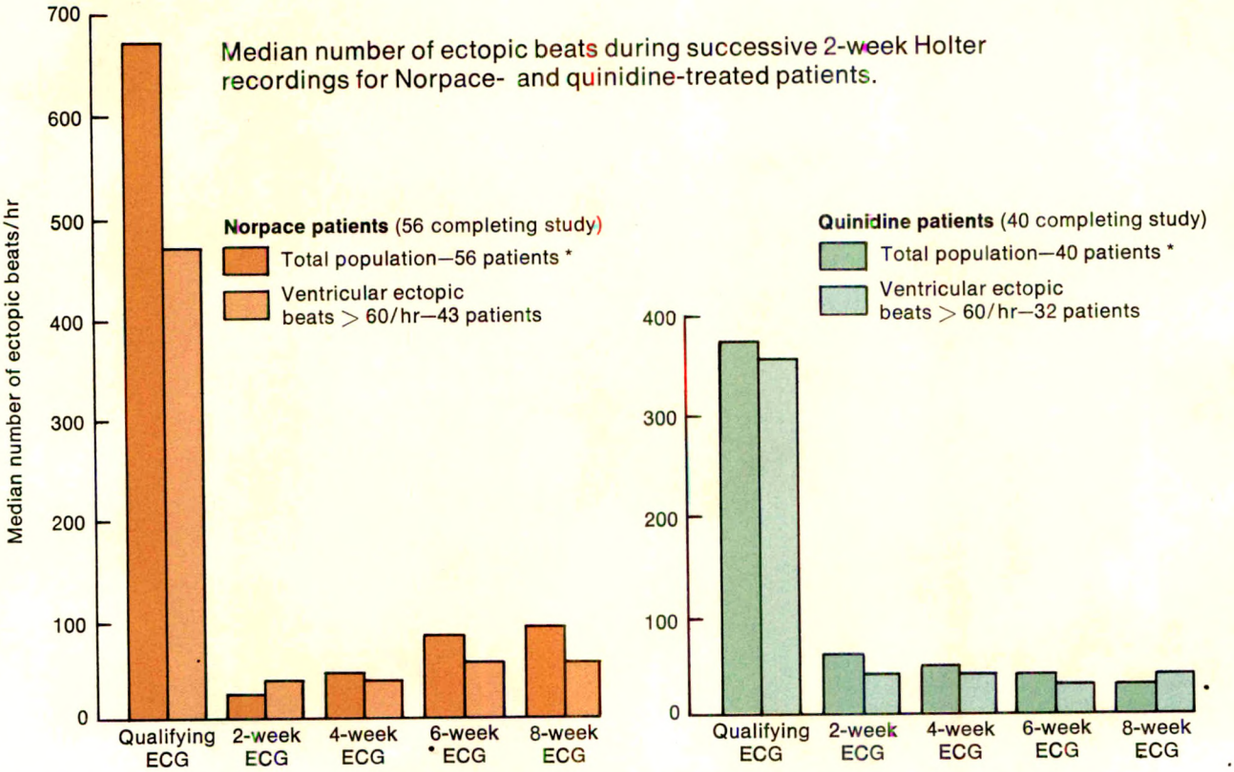
Median number of ectopic beats during successive 2-week Holter recordings for Norpace- and quinidine-treated patients.



* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

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or side effects. The side effects experi-
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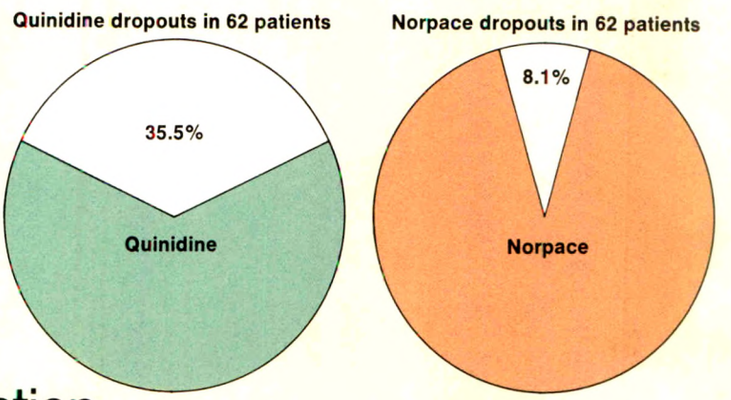

Dosage and administration

upplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response
nd tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily,
llowing an initial loading dose.

ecommended dosage regimen

Patient type	Loading dose	Maintenance dose
Adult	300 mg	150 mg q 6 h
Adults of smaller stature; or with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation	200 mg	100 mg q 6 h
Adults with severe renal insufficiency C_{cr} less than 40 ml/min	200 mg	100 mg given approximately every half-life (see Note below)

ote: Since Norpace is excreted in the urine, renal insufficiency appreciably extends the half-life of the drug. The chart below
ovides guidelines to the appropriate Norpace dosage in such patients.

orpace dosage interval adjustment for patients with renal insufficiency

Creatinine clearance (ml/min)	40-15	15-5	5-1
Approximate maintenance-dosing interval	q 10 h	q 20 h	q 30 h

orpace plasma half-life may also be prolonged in patients with significant liver disease.

ease see next page for a brief summary of prescribing information.

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as effective as quinidine sulfate for specific ventricular arrhythmias...with less severe side effects

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Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia, atrial arrhythmias or arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed on rare occasions, primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless it is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may cause cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency, dysuria. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *Central Nervous System:* nervousness, depression, insomnia, impotence, dizziness, general fatigue/muscle weakness, headache, malaise, and rarely, reversible acute psychosis. *Cardiovascular:* edema/weight gain, cardiac conduction disturbances, shortness of breath, syncope, chest pain, hypotension. *Dermatologic:* generalized rash/dermatoses.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily, following an initial loading dose. The recommended initial dosage schedule for adults is a single loading dose of 300 mg, followed by 150 mg every six hours.

For patients of small stature, or for those with moderate renal insufficiency, hepatic insufficiency, cardiomyopathy, or possible cardiac decompensation, a loading dose of 200 mg is recommended, followed by 100 mg every six hours.

For patients with severe renal insufficiency lower doses are recommended. See complete prescribing information for details.

Overdosage: No specific antidote for Norpace has been identified; treatment of overdosage should be supportive. Overdosage might be expected to produce excessive widening of the QRS complex, worsening of congestive heart failure, hypotension, varying kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects might also be observed. The electrocardiogram should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given as required. In vitro studies have demonstrated good dialyzability for disopyramide.

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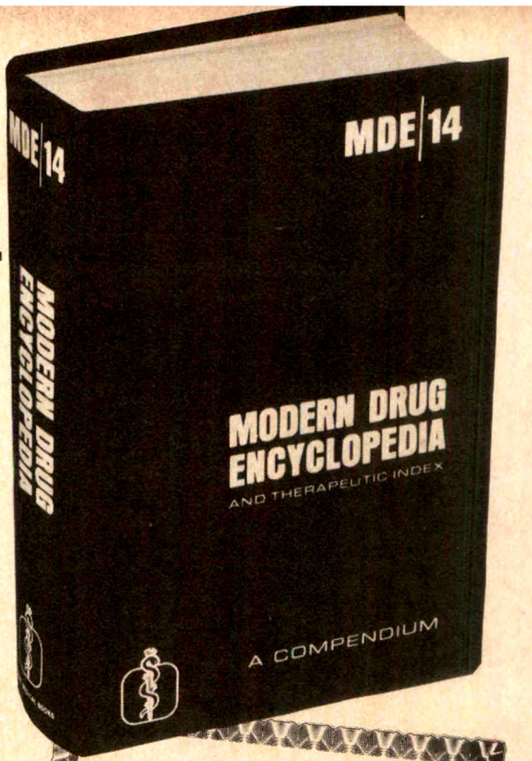

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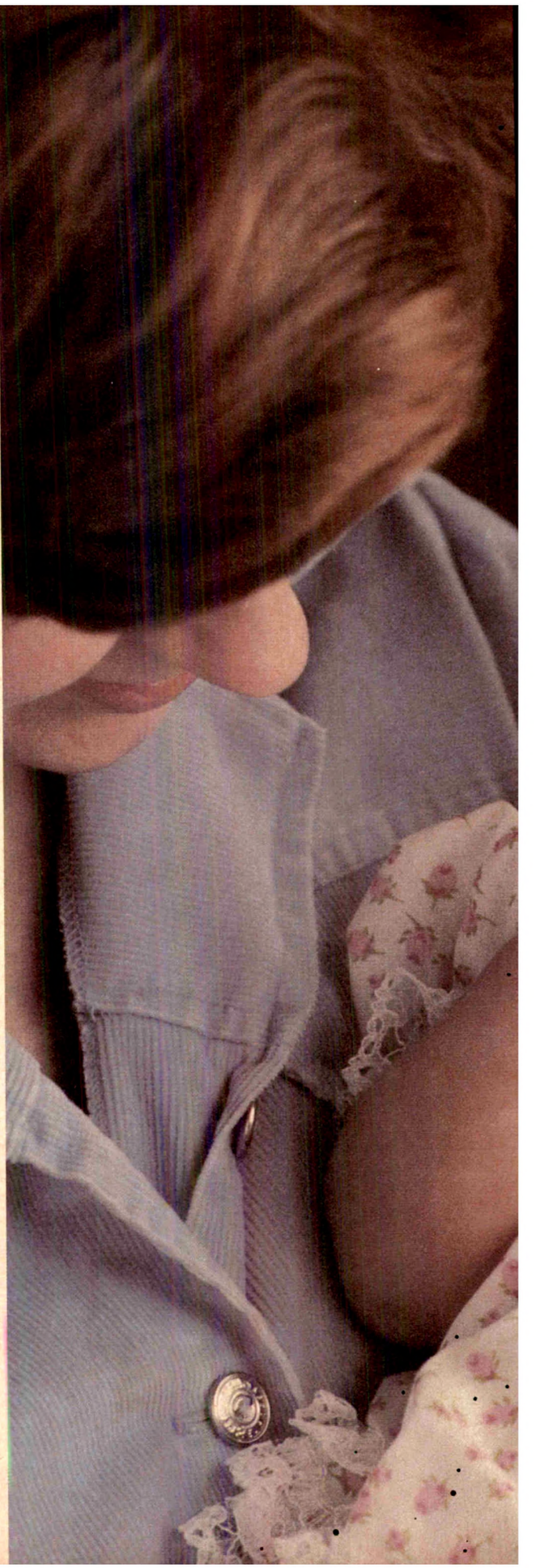

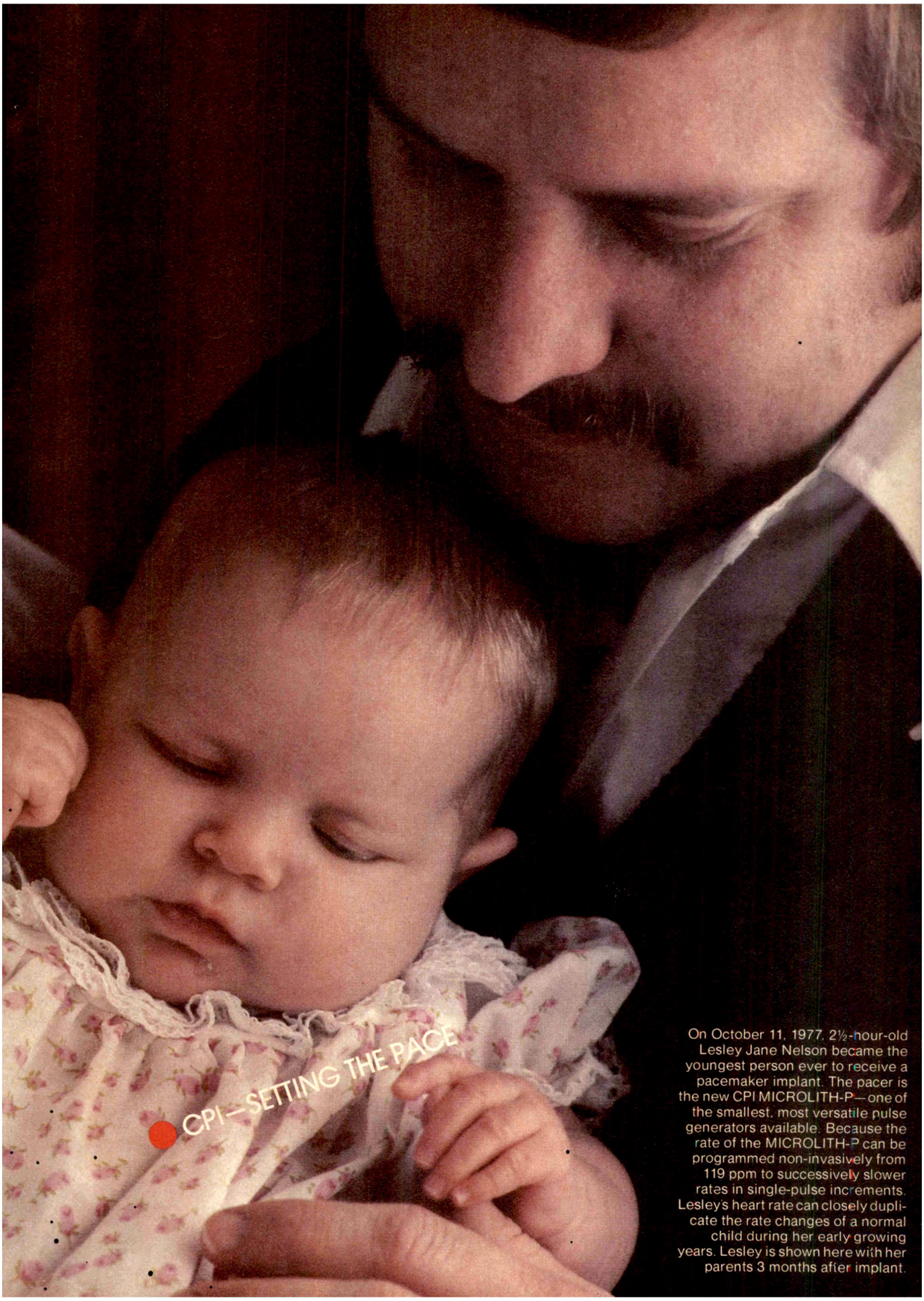

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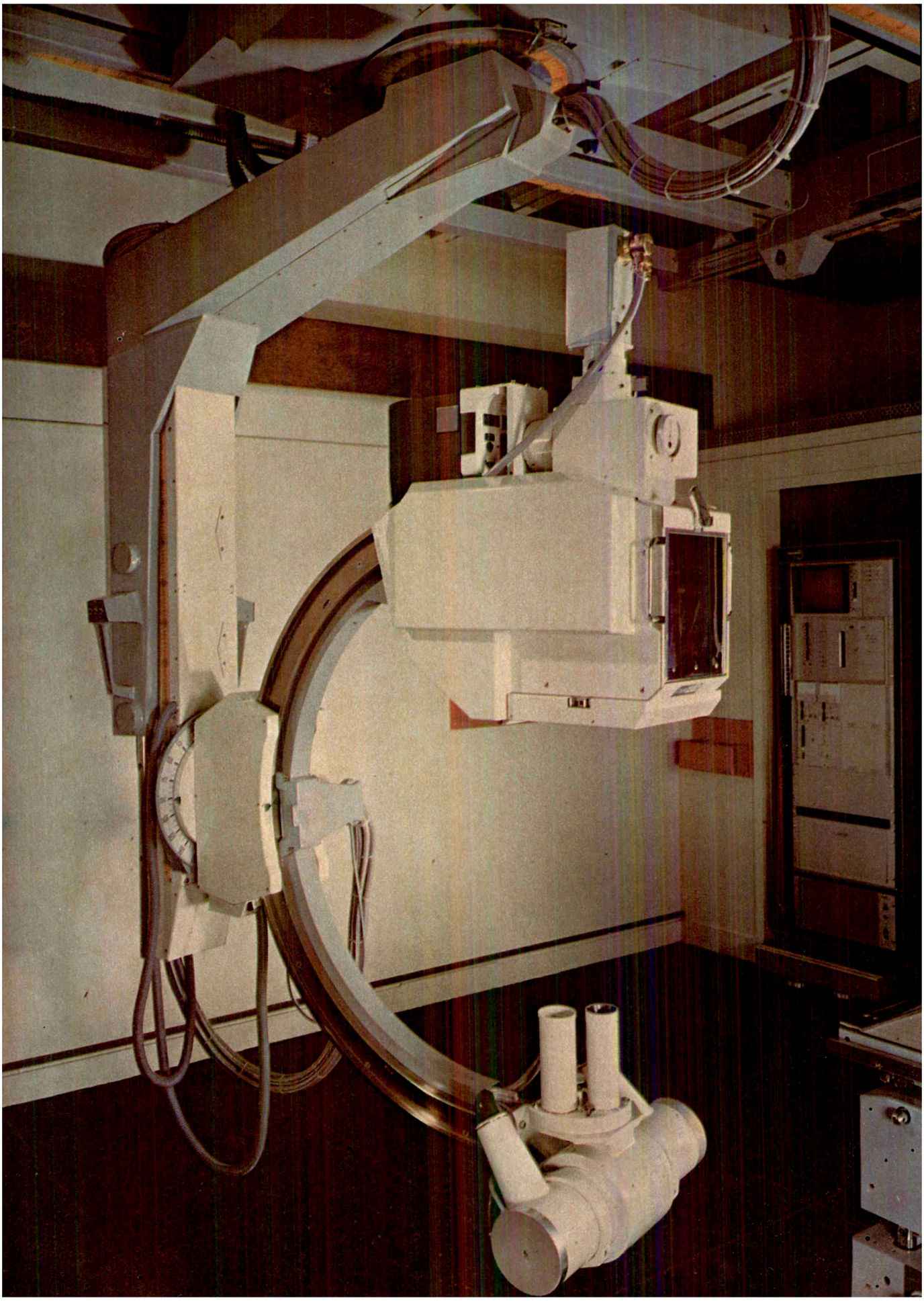

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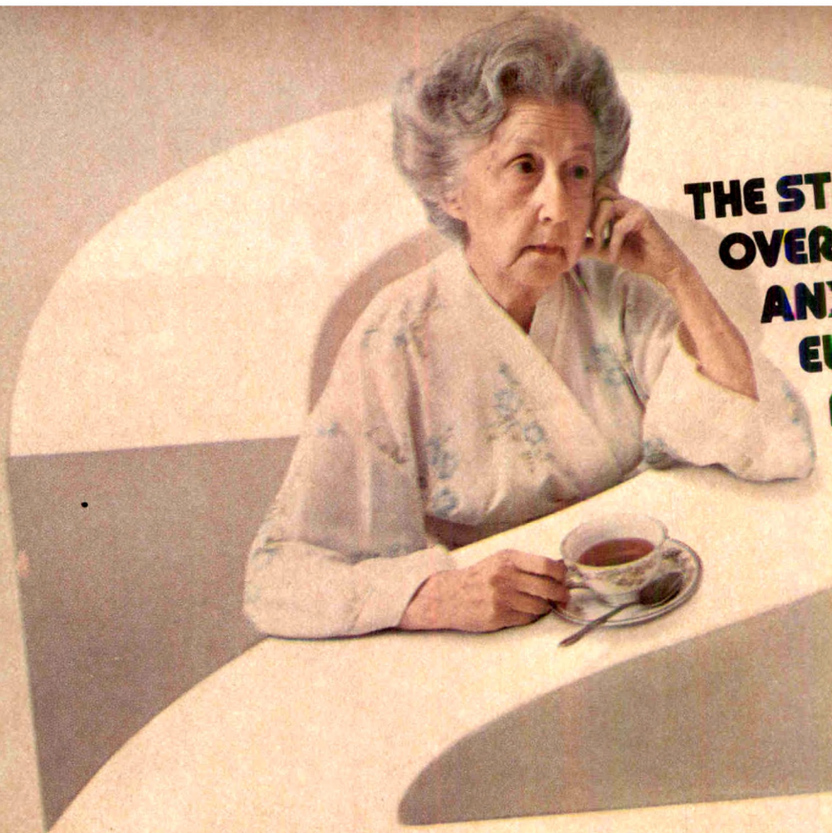

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Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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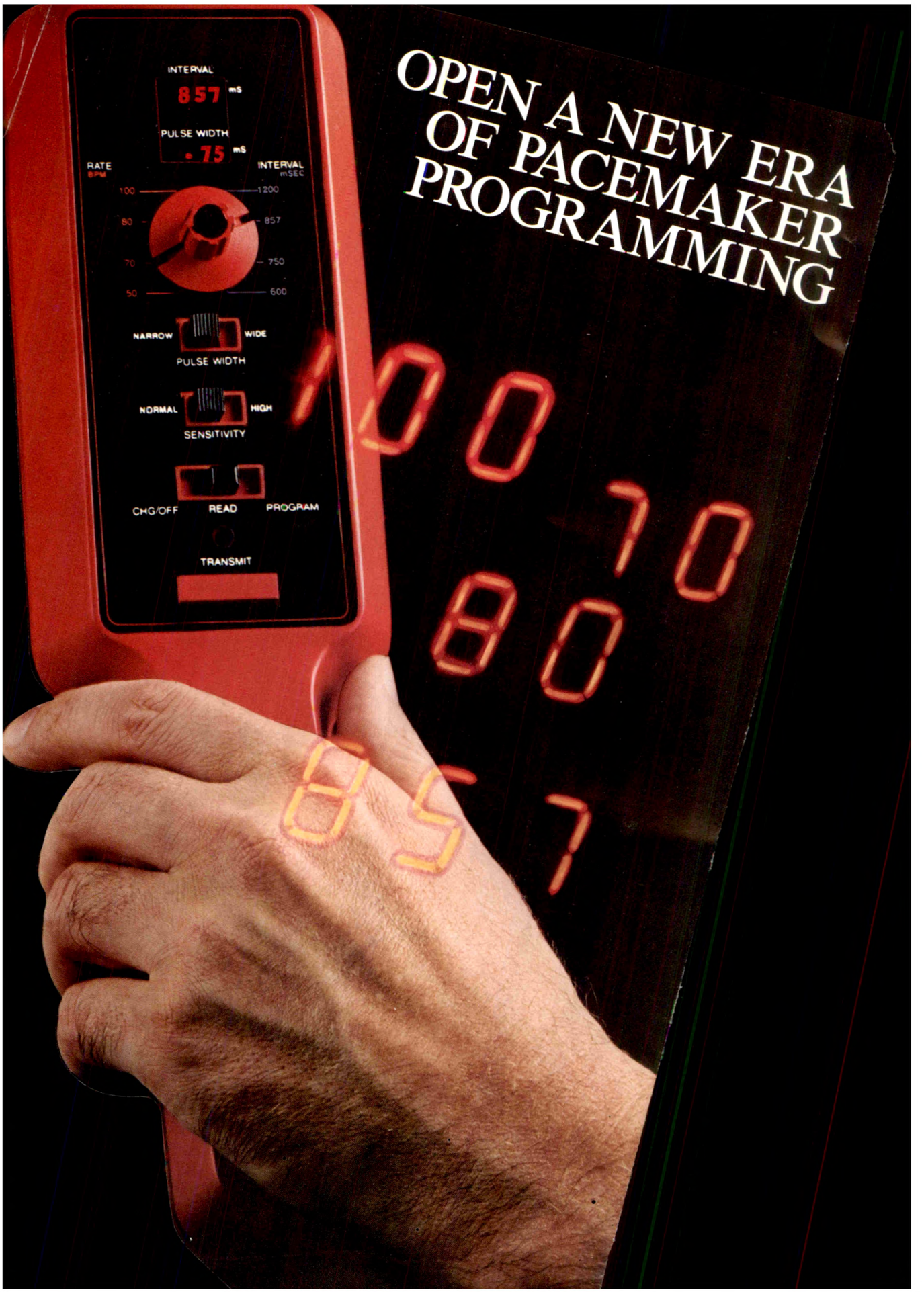
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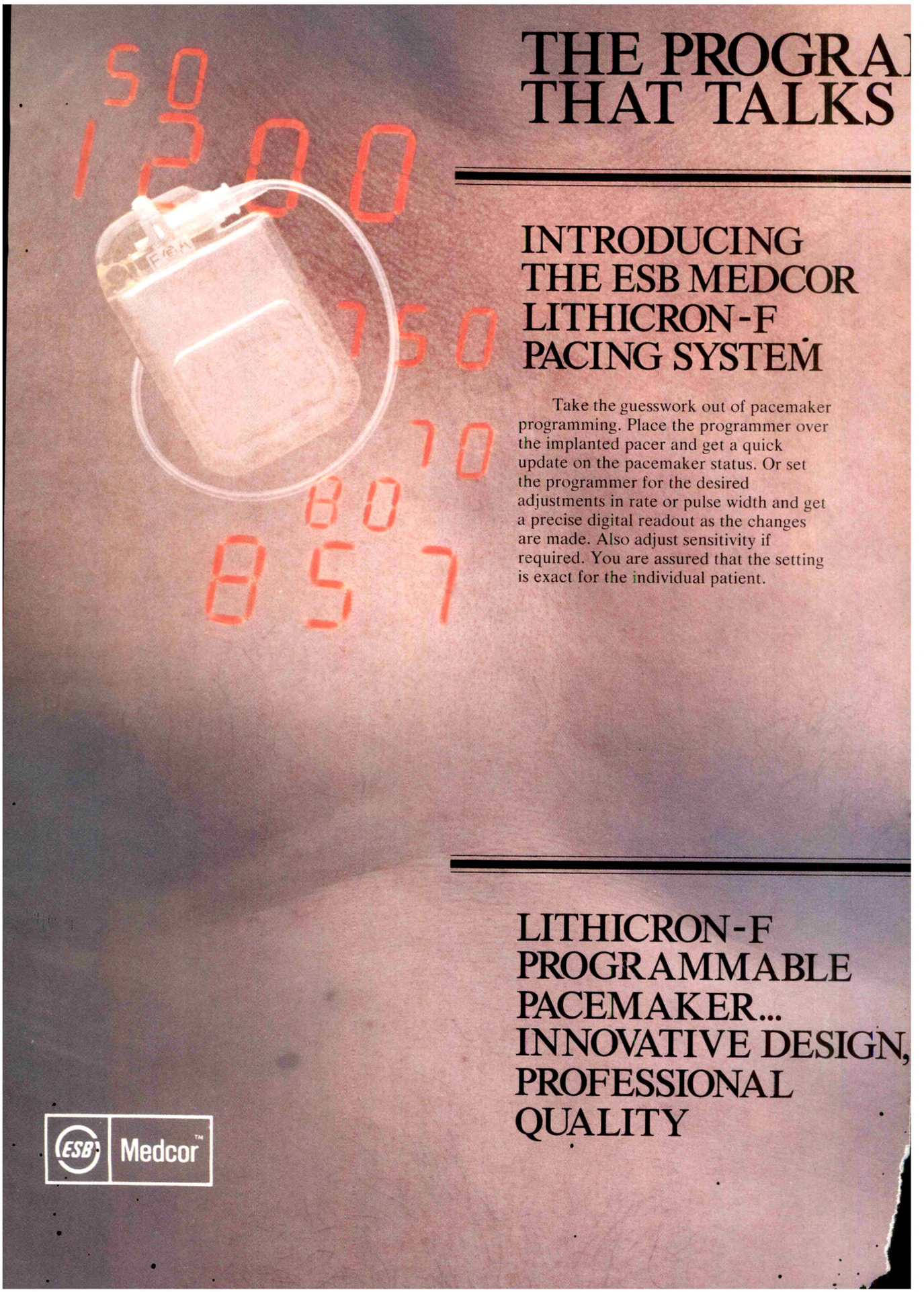

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Orally Administered Prajmalium Bitartrate in Acute and Chronic Ventricular Arrhythmias

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The effect of orally administered prajmalium bitartrate on premature ventricular complexes and on runs of such complexes was studied in 42 patients. Ventricular extrasystoles were quantified from stored continuous electrocardiographic tape recordings using a semiautomated arrhythmia-detection system. In 19 patients prajmalium bitartrate was given at a dose of 80 mg/24 hours (20 mg every 6 hours). Premature ventricular contractions decreased significantly. Two hours after administration of the drug, the frequency of premature ventricular complexes was reduced to 63 percent of the intial rate. After 6 hours the full drug effect was attained. After 12 hours the number of premature ventricular complexes averaged 30 percent of the initial value. During the succeeding drug-free interval the frequency of premature ventricular complexes increased and reached 57 percent of the initial value after 10 hours.

In a second group of 14 patients each patient was treated with prajmalium bitartrate and procainamide (3 g/24 hours) for comparison of drug effects. No significant differences were found in the antiarrhythmic action of the two drugs. Prajmalium bitartrate was well tolerated by all patients. However, three patients receiving procainamide complained of nausea and gastrointestinal symptoms and two of them had to discontinue therapy. One patient receiving long-term procainamide therapy experienced reversible joint pains of a lupus erythematosus-like syndrome.

In a third group of 23 patients with acute myocardial infarction 9 patients were given prajmalium bitartrate, 20 mg 3 times every 4 hours; 14 patients (control group) received no antiarrhythmic drug. In the control group premature ventricular complexes increased continuously up to the 10th hour after infarction and slowly decreased thereafter. Prajmalium bitartrate reduced the rate of premature ventricular complexes significantly to a mean of 4 percent of the initial value. In the untreated patients the rate decreased only to 60 percent of the initial value. Runs of premature ventricular complexes were suppressed immediately after administration of prajmalium bitartrate, whereas in the control group the frequency of such runs ranged between 80 and 140 percent of the initial value. These findings document the effective antiarrhythmic action of orally administered prajmalium bitartrate on premature ventricular complexes.

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The alkaloid ajmaline, isolated from rauwolfia serpentina, has been used as an intravenous antiarrhythmic drug.[1–3] For oral administration the chemical structure was changed: A propyl residue and tartrate acid were added to ajmaline base • (N-propyl-ajmalium hydrogen-tartrate, prajmalium bitartrate).[4]

The antiarrhythmic drugs in current use for treatment of frequent premature ventricular complexes are quinidine, procainamide, beta blocking agents and aprindine. Among these agents prajmalium bitar-

trate as a new drug excels in its rapid and lasting effect. Its efficacy when orally administered has been described by several investigators.[5–7] This study was performed to obtain quantitative data on the effectiveness, latency, time of peak effect and duration of action of prajmalium bitartrate. The action of the drug was compared quantitatively with the effect of procainamide in the same patient. It was further studied in patients with acute myocardial infarction and its effects compared with those in an untreated control group.

Patients and Methods

Three groups of patients with frequent premature ventricular complexes were investigated. Group I (19 patients) was treated with prajmalium bitartrate (Neo-Gilurytmal®, Giulini Pharma, West Germany). Group II (14 patients) was treated with prajmalium bitartrate and procainamide (Novocamid®, Hoechst AG, West Germany) for comparison of drug effects. Group III (nine patients with acute myocardial infarction) was treated with prajmalium bitartrate and the effects compared with those in 14 patients in an untreated control group.

Group I: Prajmalium Bitartrate Alone

Patients: Nineteen patients with frequent premature ventricular contractions (mean age 56 years) received prajmalium bitartrate in a dose of 80 mg/24 hours (in five cases a dose of 120 mg/24 hours). The single dose was 20 or 30 mg, respectively. Fourteen patients had coronary heart disease, nine had cardiomyopathy and two had hypothyroidism. In seven patients who had additional runs of premature ventricular complexes the therapeutic results were analyzed separately.

Protocol: Patients were selected for study when arrhythmias of a constant frequency were recorded during 48 hours. The total investigation period lasted 6 days. After a 2 day control period with no antiarrhythmic therapy prajmalium bitartrate was administered on the third and fourth days. To exclude a spontaneous remission of arrhythmia, the patients were observed without medication during the subsequent 48 hours.

Group II: Prajmalium Bitartrate Versus Procainamide

Patients: Ten patients in Group I and four other patients aged 24 to 83 years (mean 45) were treated with prajmalium bitartrate and procainamide. Prajmalium bitartrate was administered in a dose of 80 mg/24 hour (in three patients in a dose of 120 mg/24 hours) alternating with procainamide in a dose of 3 g/24 hours. Six patients had coronary heart disease, 7 had cardiomyopathy and 1 patient had terminal renal insufficiency.

Protocol: After a 6 day trial period as described in Group I, procainamide was given on the seventh and eighth days. On days 9 and 10 the patients received no antiarrhythmic medication.

Group III: Prajmalium Bitartrate Versus No Antiarrhythmic Therapy in Patients With Acute Myocardial Infarction

Patients: Patients with acute myocardial infarction who had more than 8 and less than 250 premature ventricular complexes per hour were included in this study. Patients treated with lidocaine were excluded. The patients studied reached the hospital 4.3 ± 0.8 hours (mean ± 1 standard deviation) after the onset of chest pain. Nine patients, selected at random, received prajmalium bitartrate and 14 others received no antiarrhythmic drug during a 32 hour control period.

In the treated and control groups, respectively, three and five patients had anterior and six and nine had posterior myocardial infarction; four patients in both groups had left ventricular failure and four and five patients, respectively, were receiving digitalis. Patients of both groups had similar

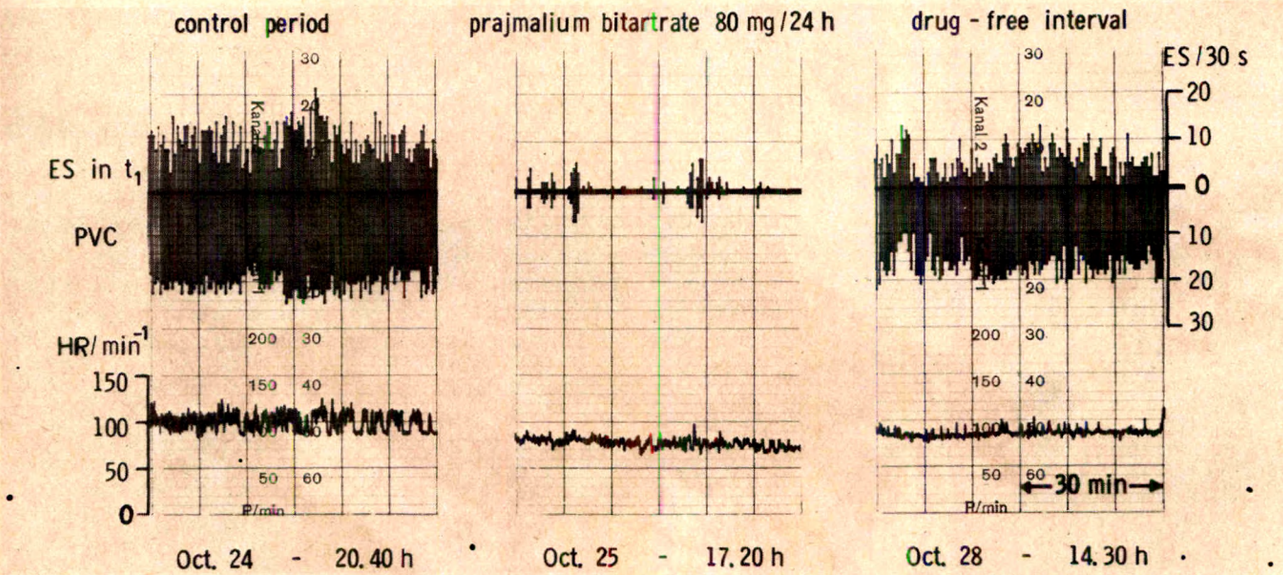

FIGURE 1. Example of effect of prajmalium bitartrate on premature ventricular complexes (PVC) as registered by trend recorder. During the control period, 2,100 premature ventricular contractions per hour were counted. Drastic reduction and a decrease in heart rate (HR) occurred with medication. An increase of premature ventricular complexes to 1,800/hour occurred during the drug-free interval. Extrasystolic beats per 30 seconds (ES/30 s) are recorded in vertical columns. h = hours; ES in t_1 = early extrasystolic beats in a given time period (t_1) from the R wave.

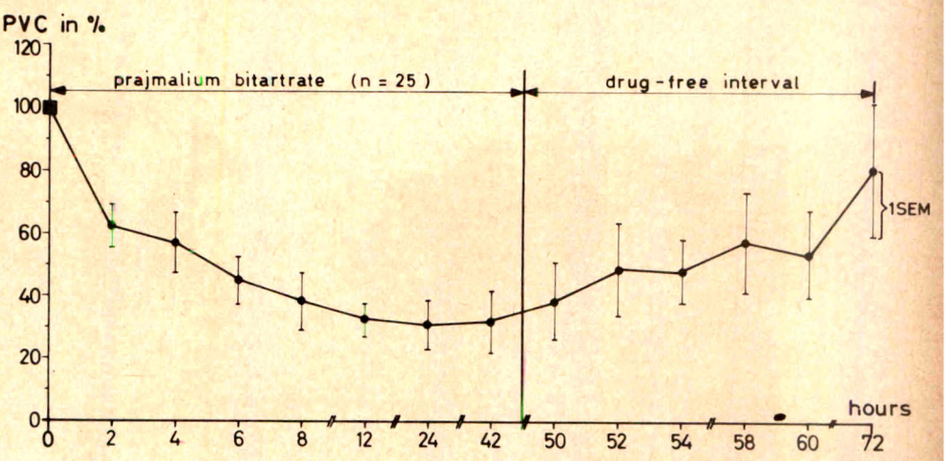

FIGURE 2. Effect of prajmalium bitartrate on premature ventricular complexes (PVC) expressed in percent of initial frequency (mean ± 1 standard error of the mean [SEM]). Premature ventricular complexes is decreased to 63 percent after 2 hours and to 33 percent after 12 hours; they increased during the drug-free interval. n = number of patients.

peak enzyme values, indicating a comparable extent of infarcted area.

Protocol: During a 6 hour control period when no antiarrhythmic drugs were administered the spontaneous frequency of premature ventricular complexes and runs of such complexes was recorded. Patients received 20 mg of prajmalium bitartrate 3 times orally every 4 hours. Thereafter, patients had no medication for 18 hours. The control group received no antiarrhythmic drug during the total 32 hour observation period.

Registration of arrhythmias: Premature ventricular complexes were quantified from stored continuous electrocardiographic tape recordings (Meditape AR, Siemens AG, Erlangen[8,9]) using a semiautomated arrhythmia-detection system. This device registers all ectopic beats, missed beats and all artifacts. All events are inscribed on a paper chart together with the last two to three normal QRS complexes stored by a special device. The recordings were analyzed by hand every or every other hour. The heart rate and the frequency of arrhythmias detected with an incorporated automatic analyzer were monitored by a trend recorder.

Results

Group I: Prajmalium bitartrate alone: In 20 of 25 patients prajmalium bitartrate was effective (Fig. 1). Premature ventricular complexes were suppressed or significantly reduced by 50 percent of the individual mean frequency during the control period. In five of seven patients with additional runs of premature ventricular complexes a significant decrease occurred with medication.

Before drug administration a fairly constant frequency of premature ventricular complexes was observed during a 48 hour control period and was listed as 100 percent (Fig. 2). After 2 hours the mean frequency was reduced to 63 percent (from 513 to 384/hour; $P < 0.025$), and after 6 hours to 45 percent (254 ± 90/hour) (Fig. 2, Table I).

During the drug-free interval the frequency of premature ventricular complexes increased to 57 percent of the initial mean value 10 hours after the last administration of the drug and to 80 percent after 24 hours.

In four of the seven patients the runs of premature ventricular complexes were completely suppressed. One woman with 40 runs of premature ventricular contractions per hour had an average of approximately 2 runs per hour with medication. In two patients, one with 16 and the other with 3 runs per hour, the frequency of the runs was reduced to less than 50 percent of the initial value. When administration of prajmalium bitartrate was discontinued, the frequency of runs increased in all patients, in some to control values.

Group II: Prajmalium bitartrate versus procainamide: Prajmalium bitartrate suppressed or significantly reduced premature ventricular complexes in 10 of 14 patients, and procainamide in 11 of 14 patients. There was no significant difference in drug effect be-

TABLE I

Frequency of Premature Ventricular Complexes in 19 Patients Treated With Prajmalium Bitartrate, 80 mg/24 hours (mean ± standard error of the mean)

Hours	Observed Values per Hour	Percent of Initial Values During Control Period
	Control Period	
24 48	513 ± 120	100
	During Medication	
2	384 ± 136	63 ± 7
4	355 ± 117	57 ± 9
6	254 ± 90	45 ± 8
8	267 ± 98	42 ± 8
10	211 ± 89	34 ± 7
12	222 ± 85	33 ± 6
18	218 ± 79	40 ± 11
24	224 ± 85	32 ± 8
36	196 ± 72	30 ± 7
42	254 ± 101	34 ± 11
	Drug-Free Interval	
2	294 ± 111	39 ± 12
4	368 ± 126	48 ± 13
6	341 ± 124	46 ± 10
10	367 ± 138	57 ± 18
12	332 ± 119	55 ± 15
24	334 ± 129	80 ± 20
36	459 ± 196	91 ± 19

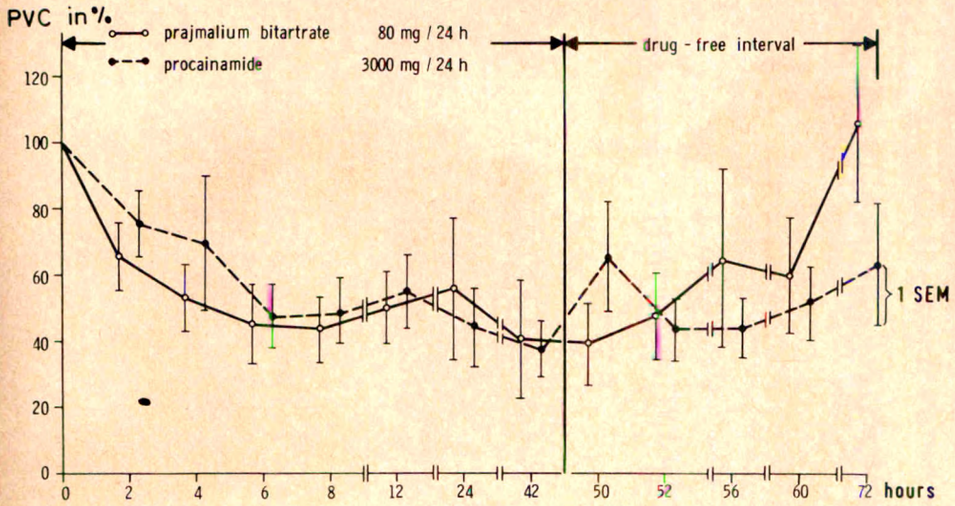

FIGURE 3. Drug effect of prajmalium bitartrate versus procainamide in 14 patients. There was no significant difference in reduction of premature ventricular complexes with either drug. Premature complexes as expressed in percent of initial frequency (mean ± 1 standard error of the mean). h = hours. PVC = premature ventricular complexes.

tween prajmalium bitartrate and procainamide (Fig. 3). Both drugs reduced the frequency of premature ventricular complexes to 40 percent of the initial value. When prajmalium bitartrate was discontinued, the frequency increased to 66 percent after 10 hours and to 106 percent after 24 hours. When procainamide was discontinued the frequency of premature ventricular complexes increased to 41 percent after 10 hours and to 73 percent after 24 hours (Fig. 3).

In four patients with additional runs of premature ventricular complexes a significant therapeutic effect was noted after administration of prajmalium bitartrate as well as after administration of procainamide. A typical example of drug effect in a 24 year old woman with cardiomyopathy and runs of premature ventricular complexes is shown in Figure 4.

Group III: Prajmalium bitartrate versus no antiarrhythmic therapy in patients with acute myocardial infarction: During the initial 6-hour control period the maximal absolute frequency of premature ventricular complexes was 50 ± 16 and 49 ± 21 (± 1 standard error of the mean) per hour in the untreated and in the treated group, respectively. Figure 5 illustrates the percent decrease of premature ventricular complexes from control values in both groups. In the untreated patients premature ventricular complexes decreased slowly. In patients treated with prajmalium bitartrate a sharp and steady decrease of premature ventricular complexes was recorded. The difference from the untreated group was particularly pronounced at the time of maximal drug effect, that is, 4 to 14 hours after drug administration (in Figure 5 between 10 and 20 hours). The frequency of premature ventricular complexes was reduced to 4 percent, whereas in the control group it spontaneously decreased to 60 percent of the initial value (16th hour).

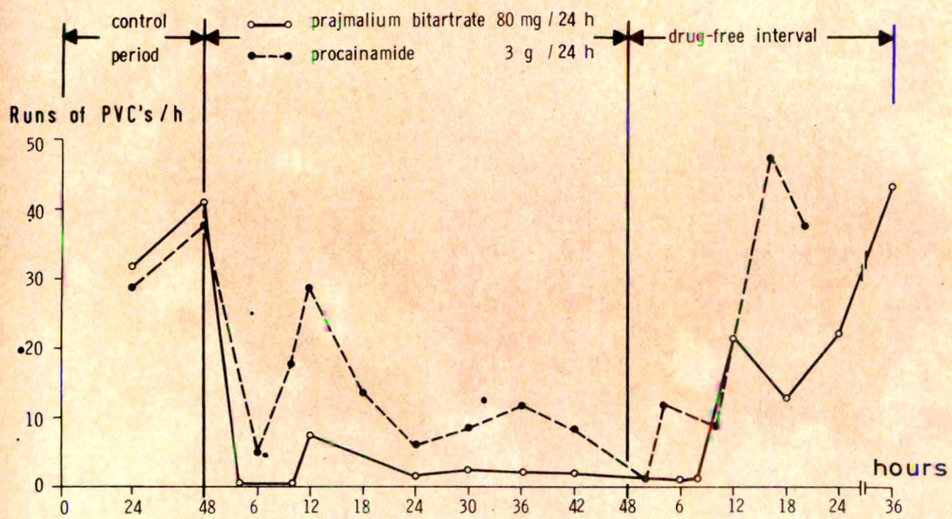

FIGURE 4. Runs of premature ventricular complexes per hour (Runs of PVC's/h) in a 24 year old patient with hypertrophic obstructive cardiomyopathy recorded before, during and after administration of prajmalium bitartrate and procainamide. Both drugs reduced pairs and runs of premature complexes; prajmalium proved to be more effective. An increase in the rate of runs occurred when the drugs were discontinued.

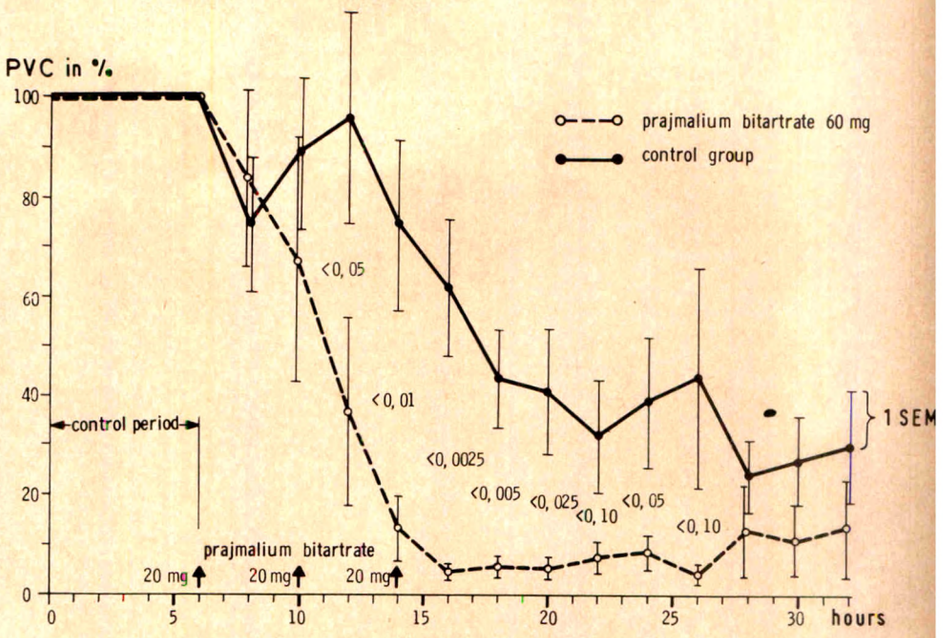

FIGURE 5. Premature ventricular complexes in 23 patients with acute myocardial infarction, treated with prajmalium bitartrate, and 14 (control group) given no antiarrhythmic therapy. The frequency of premature ventricular complexes (PVC) is expressed in percent of values in the control period. **Arrows** indicate oral administration of 20 mg of prajmalium bitartrate. There is a significant sharp decrease of premature ventricular complexes in the treated group compared with that in the control group.

The percent frequency of runs of premature ventricular complexes compared with that in the 6 hour control period is illustrated in Figure 6. In the untreated patients the frequency of runs of premature ventricular complexes increased to 260 percent of the initial value. Thereafter, such runs decreased discontinuously with interspersed elevated rates. Individual values in the untreated patients differed markedly. In patients treated with prajmalium bitartrate, runs of premature ventricular complexes decreased immediately with medication. A significant difference in the course of treated and untreated patients was noted earlier than in the corresponding groups with premature ventricular complexes (2 hours with medication, $P < 0.1$; 4 hours with medication, $P < 0.05$). The peak effect was reached after 4 hours, when the frequency of runs of premature ventricular complexes per hour was 37 percent of initial values in the treated and 255 percent in the untreated

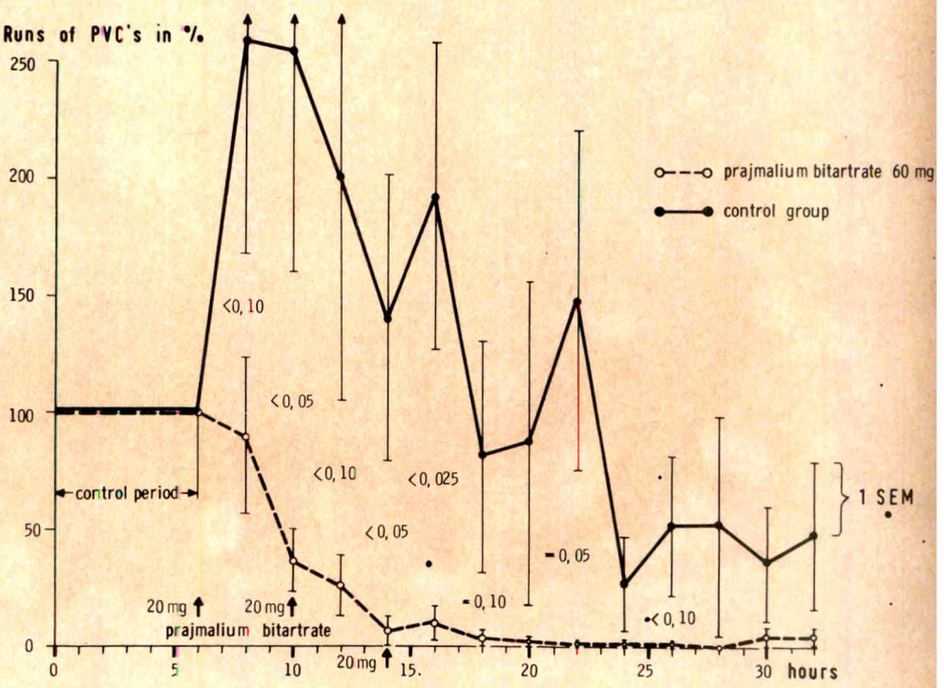

FIGURE 6. Runs of premature ventricular complexes in 23 patients with acute myocardial infarction, 9 treated with prajmalium bitartrate and 14 given no antiarrhythmic therapy. The frequency of runs of premature ventricular complexes (PVC's) is expressed in percent of values in the control period. **Arrows** indicate oral administration of 20 mg of prajmalium bitartrate. There is almost complete suppression of runs of premature ventricular complexes in the treated group in contrast to the spontaneous occurrence of runs in the control group.

patients. Eight hours after the first administration of prajmalium bitartrate (that is, during the 14th hour) (Fig. 6), runs of premature ventricular complexes were almost completely suppressed (6 percent), whereas in the untreated patients frequencies of 140 percent of initial values were observed.

Side effects: During the 48 hour treatment period patients in Groups I and II treated with prajmalium bitartrate did not complain of gastrointestinal disorders. In 2 of 11 patients with left ventricular failure, moist rales and dyspnea tended to increase. The condition of one of these patients seemed to improve with an increased digitalis dose. The second patient showed symptoms only at the end of the 48 hour medication period, and they decreased when the drug was discontinued. One 62 year old woman showed evidence of the negative dromotropic effect due to hypothyroidism[6,7] with a consecutive atrioventricular block. After discontinuation of the drug, normal rhythm was restored. With procainamide three patients were nauseated and had gastrointestinal complaints, forcing two of them to discontinue medication. Another 38 year old patient complained of arthritic pain, particularly in his knee joints, after 20 days of procainamide therapy. These lupus erythematosus-like manifestations are a known side effect.[10–12]

Patients of Group III experienced no significant side effects with prajmalium bitartrate.[13] Four of the treated patients had left heart failure before therapy and their condition did not deteriorate during drug administration.

Discussion

Mechanism: The antiarrhythmic effect of prajmalium bitartrate is based on the suppression of the spontaneous activity of pacemaker cells on prolongation of the refractory period and reduction in conduction velocity in the Purkinje fibers.[14,15] The A-H interval of the His bundle electrogram is not affected but the H-V interval is considerably prolonged.[16] Because of these electrophysiologic properties prajmalium bitartrate plays an important role among antiarrhythmic agents, especially in acute and chronic ventricular arrhythmias.

Chronic arrhythmias: From continuous long-term observations and analysis of electrocardiograms, we obtained quantitative data on the frequency of ventricular arrhythmias before and during prajmalium bitartrate therapy. In 80 percent of the patients in Group I, premature ventricular complexes were suppressed or significantly reduced. These findings are fairly similar to the results of others.[5,6] Dransfeld[17] as well as Mathey et al.[7] reported positive results in 70 percent of the patients on the basis of data registered by trend recorder.

The frequency of premature ventricular contractions decreased significantly 2 hours after administration of 20 mg of prajmalium bitartrate. With conversion of the data to 1 hour, a decrease of 20 percent resulted. The maximal effect was almost reached after 6 hours. During the drug-free interval, premature ventricular complexes increased considerably after 10 hours. Koch[6] found a duration of action of 8 1/2 hours based on the recurrence of premature ventricular complexes. The mean effective dose was 80 mg/24 hours, administered in four single doses of 20 mg. More than 120 mg/24 hours was never given because of the drug's known negative dromotropic effect.[7,17–19]

Comparison with procainamide: In the comparative study of drug action prajmalium bitartrate and procainamide proved equally effective (Group II). Prajmalium bitartrate was well tolerated by all patients, whereas three had to discontinue procainamide because of gastrointestinal side effects. Long-term therapy with procainamide is known to cause agranulocytosis as well as lupus erythematosus-like symptoms.[10,11,12,18] According to published reports,[5–7,13] prajmalium bitartrate affects the heart and the gastrointestinal tract only. However, it may also induce an intrahepatic cholestasis.[7] Prajmalium bitartrate is an effective oral antiarrhythmic drug. It excels among similar agents because of the smaller effective absolute dose, and the fewer side effects.

Acute myocardial infarction: Our results indicate that prajmalium bitartrate reduces and in some cases suppresses premature ventricular complexes and runs of these complexes in the acute phase of myocardial infarction. The untreated group with infarction manifested a spontaneous reduction in frequency of ventricular premature complexes to 60 percent of initial values, whereas the treated group had a reduction to 4 percent. Runs of premature ventricular complexes were almost completely reduced during prajmalium bitartrate therapy, whereas a frequency of 82 to 240 percent of the initial value was recorded in the untreated group.

The onset of drug effect was noted after 1 hour when the frequency of premature ventricular complexes and runs of these complexes was reduced by 10 percent. The drug effect continued for about 8 hours. These findings confirm the results on latency and duration of action reported by other investigators in patients without myocardial infarction.[6,13,19] In our study a relatively large dose was administered in a 24-hour period; within 8 hours 60 mg was given. The routine dose of prajmalium bitartrate is approximately 80 mg/24 hours.[6,19]

A homogenous group of patients with acute myocardial infarction was separated at random into a treatment group and an untreated control group. A similar extent of infarction was assumed in all patients on the basis of comparable peak serum enzyme values. Spontaneous premature ventricular complexes occurred with similar frequency in both groups during the control period. All patients were about the same age and had the same serum potassium values. Moreover, the number of digitalized patients with heart failure was equally large in both groups. Thus, both groups were statistically comparable.

Life-threatening arrhythmias in acute myocardial infarction should preferably be treated with an intravenous antiarrhythmic drug for immediate onset of

effect.[20] In these cases lidocaine is often used because of its mild negative inotropic effect.[21,22] However, the findings on its effectiveness vary.[23–26]

Implications: Oral administration of prajmalium bitartrate for persistent ventricular arrhythmias and for arrhythmias in acute myocardial infarction effectively reduces or suppresses premature ventricular complexes and runs of these complexes. Side effects during short-term administration are not observed. The drug seems to have advantages over other antiarrhythmic agents such as quinidine[27–29] and procainamide.[18,30]

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Coronary Revascularization Under Age 40 Years

Risk Factors and Results of Surgery

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Groups of patients such as the elderly, the diabetic and women have been studied to evaluate the effectiveness of coronary revascularization. In this report 77 patients under age 40 years undergoing coronary revascularization were studied. There was a high prevalence rate of predisposing factors. Sixty-eight percent reported a family history of heart disease and 27 percent a history of diabetes; 57 percent were hypertensive, 43 percent were overweight, 91 percent smoked, 5 percent were diabetic and 16 percent had abnormal glucose tolerance curves. Sixty-four percent had hypercholesterolemia (cholesterol 250 mg/100 ml) and 56 percent hyperlipidemia. Forty-four percent had had a previous myocardial infarction; 95 percent had angina pectoris, 12 percent preinfarction angina and 9 percent congestive cardiac failure. There were no operative deaths. The incidence rate of perioperative myocardial infarction (new Q waves in the electrocardiogram) was 4 percent. The mean length of follow-up was 26 months (range 6 months to 5 years). The late mortality rate was 4 percent. Eight percent had a late myocardial infarction. Overall graft patency was 85 percent. Sixty-seven percent of patients were free of angina, and 17 percent were in improved condition. Seventy-one percent returned to work, while 29 percent remained unemployed. This study shows that in young patients, coronary revascularization is associated with low mortality and morbidity rates and that, despite the wide prevalence of predisposing factors, the prognosis and graft patency rate of these patients are similar to those of other groups.

Studies to evaluate the effectiveness of coronary revascularization have reported on various groups of patients, such as the elderly,[1,2] the diabetic[3] and women.[4] The observation of coronary artery disease in young people has increased in recent decades, and there have been several recent reports of myocardial infarction in young patients.[5–8] This group is of special interest in evaluating the risk-benefit ratio of coronary revascularization. Surgery may be more effective and important for rehabilitation in young patients, who are usually employed and vigorous, than in older patients. Although the risk of surgery in young people is less, the presence of predisposing factors may have an adverse effect on graft patency and progression of disease. To evaluate the effectiveness of coronary revascularization in the young, we reviewed the pre- and postoperative status of 77 patients under age 40 years who underwent coronary revascularization.

Material and Methods

From July 1971 to June 1976 a total of 77 patients under age 40 years underwent coronary revascularization at this medical center. All of these patients, 70 men and 7 women, are included in this study. There were 46 patients aged 36 to 40 years, 23 aged 31 to 35 years, 6 aged 26 to 30 years and 2 aged 20 to 25 years.

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TABLE I

Preoperative Status of 77 Patients Under the Age of 40 Years Undergoing Coronary Revascularization

	Patients	
	no.	%
Previous myocardial infarction		
0	43	56
1	24	31
2	10	13
Angina pectoris, class		
I	6	7
II	19	25
III	28	36
IV	21	27
No angina	3	4
Preinfarction angina	9	12
Congestive cardiac failure	7	9

Preoperative status: Seventy-four patients had angina pectoris (Table I). They were classified according to the criteria of the New York Heart Association.[9] Six were in class I, 19 in class II, 28 in class III and 21 in class IV. Three patients did not have angina pectoris but had a history of previous myocardial infarction or a strong family history of early sudden death. Thirty-four patients had a history of myocardial infarction, and 10 of these had had two infarcts. Nine patients were operated on after an episode of preinfarction angina. Seven had congestive cardiac failure. Ten patients were employed in sedentary occupations; 17 were supervisors or managers. Fifteen worked at jobs requiring moderate physical exertion, such as carpentry and electrical work, and 34 had jobs requiring heavy exertion, such as construction work and farming.

Predisposing factors: Every patient in this series had at least one of these six predisposing factors: family history of heart disease, smoking, hypertension, obesity, diabetes, hypercholesterolemia or hyperlipidemia (Table II). Only 19 (25 percent) did not have a family history of diabetes or heart disease. Sixty-eight patients (91 percent) had a history of smoking more than 1 pack/day; 2 patients had smoked 1/2 pack/day. Twelve patients had no predisposing factor other than smoking. Sixteen were previously diagnosed as hypertensive. However, review of the preoperative blood pressure recordings revealed that 12 patients (15 percent) had a diastolic pressure greater than 90 mm Hg, 27 (38 percent) a systolic pressure greater than 140 mm Hg and 3 (4 percent) a systolic pressure greater than 160 mm Hg. The prevalence of obesity, shown in Table II, is based on ideal weights taken from life insurance tables.[10] The average height for men was 178 cm and for women 162 cm. The average weight for men was 84.3 kg, which is 10 percent above the average for their age and height.[10] The average weight for women was 61.2 kg, which is 9 percent above the average.[10]

Angiographic findings: Ventricular function was classified as mildly, moderately or severely impaired on the basis of the ventriculogram. In the right anterior oblique view, the heart was divided into anterior, apical and posterior segments. Mild impairment was defined as mild dyssynergy of two segments or moderate dyssynergy of one segment; moderate impairment was defined as moderate dyssynergy of two segments or severe dyssynergy of one segment. Severe impairment was defined as severe dyssynergy of two or more segments. Thirty-five patients had a normal ventriculogram, 23 (30 percent) had mild impairment, 18 (22 percent) moderate impairment and 10 (13 percent) severe impairment. An obstructive lesion greater than 70 percent of luminal diameter was considered significant. Five patients had 50 to 70 percent stenosis of the left main coronary artery, and five had greater than 70 percent obstruction of this artery. Thirty (39 percent) had single vessel disease, 19 (25 percent) double vessel disease and 27 (35 percent) triple vessel disease. One patient (1 percent) had quadruple vessel disease.

TABLE II

Predisposing Factors in 77 Patients

	Patients	
	no.	%
Family history		
Heart disease	53	68
Diabetes	21	27
Hypertension		
Diastolic >90 mm Hg	12	15
Systolic >140 mm Hg	27	38
Systolic >160 mm Hg	3	4
Obesity		
>10% above average	16	21
>20% above average	17	22
Smoking	68	91
Diabetes		
Treated	3	5
Chemical (2 hour sugar >150 mg/100 ml)	10	16
Hypercholesterolemia		
250 mg/100 ml	26	34
300 mg/100 ml	23	30
Hyperlipidemia		
Type II	14	20
Type IV	28	36

TABLE III

Number of Vessels Grafted and Graft Patency

Grafts (no.)	Patients (no.)	Patent Grafts				
		4	3	2	1	0
4	1	1	...	...	...	...
3	19	...	12	5	2	...
2	33	...	...	20	11	2
1	16	...	...	...	13	3

Operative procedure: Revascularization was performed with the patient on cardiopulmonary bypass and use of a hemodilution prime and moderate hypothermia (28° C). The number of patients having one to four grafts is shown in Table III. The reversed saphenous vein graft was generally used for the grafts to the left circumflex and right coronary arteries. Recently, the left internal mammary artery has been used for the left anterior descending coronary artery. One hundred vein grafts and 26 internal mammary artery grafts were performed (Table IV).

Results

Results of surgery: There were no operative deaths. Only one patient had a low output state requiring intraaortic balloon counterpulsation. The incidence rate of perioperative myocardial infarction diagnosed by the presence of Q waves in the electrocardiogram was 3.8 percent (3 of 77 patients).

Postoperative angiography: Sixty-nine patients had repeat catheterization within 6 months of surgery, including 44 of the 60 patients followed up for 1 year, 14 of 33 patients followed up for 3 years and 3 of 15 pa-

TABLE IV

Patency for Vein Grafts and Internal Mammary Artery Grafts at 6 Months, 1, 3 and 5 Years (Only Latest Catheterization Included)

	6 Months			1 Year			3 Years			5 Years		
		Patent			Patent			Patent			Patent	
	no.	no.	%	no.	no.	%	no.	no.	%	no.	no.	%
Vein grafts												
Right coronary artery	42	35	86	24	19	79	6	4	67	2	1	50
Left anterior descending coronary artery	33	30	91	27	21	77	11	10	91	3	2	67
Circumflex coronary artery	22	17	77	14	9	64	5	4	80	2	1	50
Diagonal branch of the circumflex coronary artery	3	3	100	3	2	67	1	1	100	...	...	...
Internal mammary artery												
Left anterior descending coronary artery	30	29	97	18	17	94	4	4	100	...	...	...
Right coronary artery	5	5	100	5	5	100	1	1	100	...	...	...
Diagonal branch of the circumflex coronary artery	1	1	100	...	...	...	...	...	...	...	...	...

tients followed up for 5 years. Left ventricular function (Fig. 1) was improved postoperatively in the majority of patients (61 percent) and showed deterioration in 4 percent of patients at 6 months. At 3 and 5 years, too few patients were catheterized to draw conclusions. With respect to the postoperative graft patency (Fig. 2, Tables III and IV), the internal mammary artery appears to be less obstructed than the vein grafts, but the difference is not statistically significant. Only five patients had all grafts occluded. Evaluation of the progression of disease at the proximal lesion (Fig. 3) revealed an increase in the number of lesions that progressed to total obstruction.

Follow-up: Patients were followed up for a mean of 26 months (6 months to 4 years) (Table V). Overall, 52 patients (67 percent) were free of angina postoperatively although only 3 patients (4 percent) had had no angina preoperatively. The condition of 13 (17 percent) was improved although they had mild angina; the angina was unchanged in 6 (8 percent) and worse in 6 (8 percent). Figure 4 shows relief of angina at various postoperative intervals. There is a reduction in the percent of patients whose angina was decreased or abolished as the follow-up is extended to 3 and 5 years. Two patients underwent reoperation 1 and 5 years after the initial procedure. In one, a vein graft to the left anterior de-

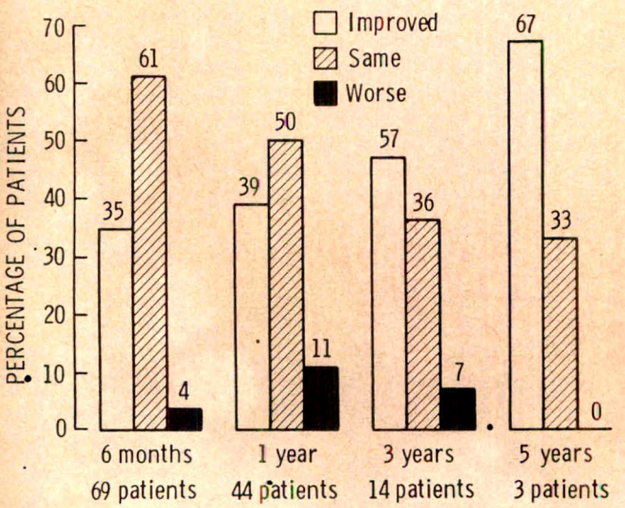

FIGURE 1. Postoperative ventricular function compared at 6 months and 1, 3 and 5 years. The number of patients studied with cardiac catheterization at each interval is shown.

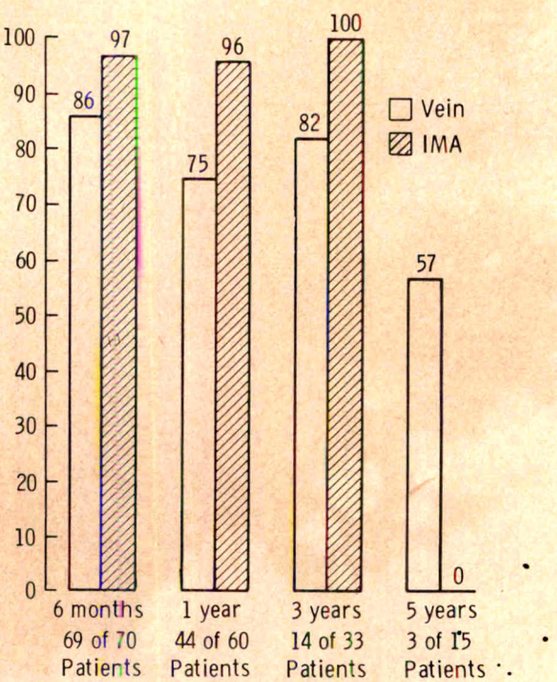

FIGURE 2. Patency of vein and internal mammary artery (IMA) grafts at various postoperative intervals. The number of patients studied with cardiac catheterization and the number followed up at each time interval is shown.

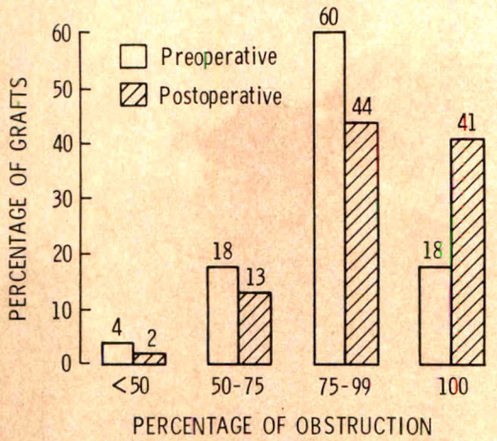

FIGURE 3. Progression of the major stenotic lesion proximal to the graft. The number of lesser degrees of obstruction decreases, as the more severe lesions progress to occlusion. The number of complete occlusions increases.

TABLE V

Long-Term Follow-Up* of Patients Under Age 40 Years Undergoing Coronary Revascularization

	Patients	
	no.	%
Late mortality	3 of 77	3.9
Myocardial infarction (postoperative)		
1 year	1	. . .
2 years	2	. . .
3 years	1	. . .
4 years	2	. . .
5 years	0	. . .
Occupation		
Returned to previous occupation	43	62
Lighter work	6	9
Unemployed	20	29
Activities		
Vigorous sports	9	13
Unrestricted	35	50
Restricted		
Mild	12	18
Severe	13	19

* Mean 26 months; range 5 months to 5 years.

scending artery became occluded and was successfully regrafted with patency demonstrated 4 years later. The second patient had recurrence of angina 5 years after grafts to the left anterior descending and circumflex arteries. Progression of disease in the right coronary artery and recurrence of angina prompted a vein graft to the right coronary artery, with patency of all three grafts demonstrated 1 year later. Both patients are asymptomatic and have returned to work.

The late mortality rate was 3.8 percent (3 of 77 patients). One patient died suddenly from presumed cardiac events 3 and 4 years postoperatively. Six patients had a myocadial infarction at intervals shown in Table V. The cumulative 5 year mortality rate, calculated with the life table method, was 8 percent (Fig. 5).

With respect to rehabilitation (Table V), 62 percent returned to their previous occupations, 9 percent returned to lighter work and 29 percent were unemployed. Sixty-three percent either engaged in vigorous sports or were not restricted in their activities.

Discussion

Incidence of risk factors: As expected, there was a high prevalence rate of predisposing factors in our patients, similar to that found by others in young patients sustaining a myocardial infarction.[5] A family history of heart disease was found in 68 percent and of diabetes in 27 percent of patients; only 25 percent did not have a positive family history of one of the two. Engel et al.[7] found a positive family history of heart

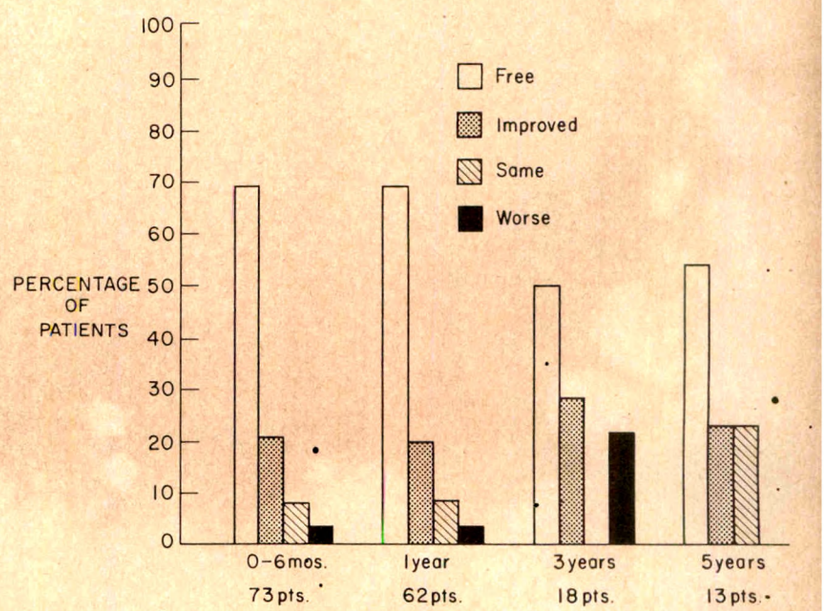

FIGURE 4. Relief of angina after surgery. The number of patients (pts.) followed up to each time interval is shown. The number of patients free of angina decreases; while the number of patients who are worse increases during the 5 year follow-up.

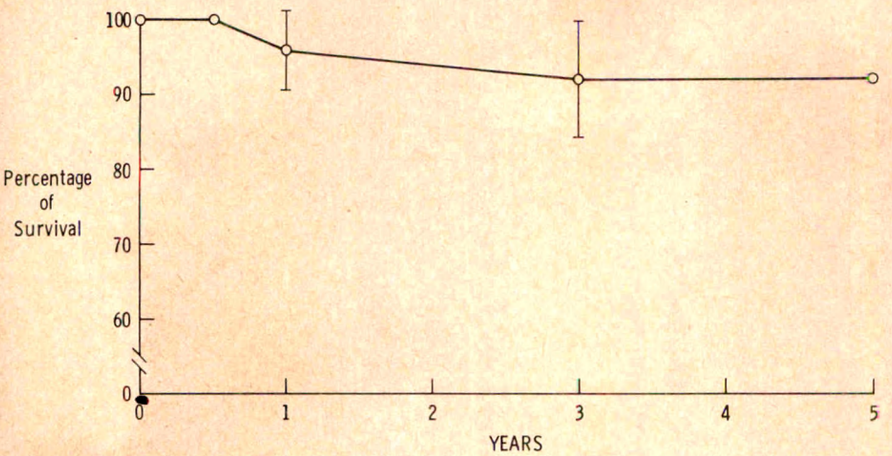

FIGURE 5. Five year survival rate calculated by the actuarial method. The cumulative 5 year mortality is 8 percent. The **vertical bars** indicate the 95 percent confidence interval obtained by adding ± 2 standard errors to the survival rate.

disease, diabetes or hypertension in 95 percent of their young women with coronary artery disease. Smoking was a strong factor in our series, with 91 percent giving a positive history, similar to the incidence rate in some reports[6] but higher than that of others.[7,11] The prevalence rates of obesity (43 percent), hypertension (54 percent), hyperlipidemia (56 percent) and hypercholesterolemia (64 percent) were similar to those reported by other authors.[3,5–8,12] The prevalence rate of diabetes (21 percent) was less than the 52 percent found by Engel et al.[7] in women with coronary artery disease under the age of 40 years.

Left ventricular function and extent of coronary disease: In our series, 35 percent of patients had normal ventriculograms and 30 percent, 22 percent and 13 percent, respectively, had mild, moderate or severe impairment preoperatively. These percentages are similar to those reported by others.[1,3] Hamby et al.[1] compared ventricular function in patients under and over age 65 years undergoing revascularization and did not find a significant difference between the two groups. A study of a group of diabetic patients undergoing revascularization also showed no difference in ventricular impairment between this group and other patients,[3] and a comparison of men and women showed no difference between the sexes.[4] Despite the young age of the patients in our study, the frequency of ventricular impairment appears to be similar to that of other groups undergoing revascularization. In our series, 39 percent had single vessel disease. Savaran et al.[13] found that 51 percent of a group of patients under 40 years of age had single vessel disease, as opposed to 33 percent in the age-unrestricted series of Proudfit et al.[14] and 42 percent reported by Gensini and Kelley.[15] Welch et al.[16] reported 43 percent of women under 50 years of age to have single vessel disease. The distribution of single vessel disease in our series therefore appears to be similar to that in other series of patients undergoing cardiac catheterization for coronary artery disease.

The distribution of the number of vessels grafted is similar to that reported by Kouchoukos et al.[17] for an age-unrestricted series of patients undergoing revascularization. Ashor et al.[2] reported a similar distribution in a series of patients over age 65 years undergoing surgery. No significant difference was shown between the number of vessels grafted in diabetic patients compared with control subjects[3] or in women compared with men.[4]

Surgical results: The patients tolerated the procedure well. There were no operative deaths although the series included 9 patients with preinfarction angina and 10 with severely impaired ventricular function. This finding compares favorably with the mortality for age-unrestricted patients undergoing revascularization.[17–19] Two groups[1,2] reported a 6 percent mortality rate for patients over age 65 years undergoing revascularization; the mortality rates have been reported as 7.1 percent in women versus 2.9 percent in men[18] and 9 percent and 4 percent, respectively, for a series of diabetic and nondiabetic patients.[3] The absence of early deaths in our series also compares favorably with the 4 percent mortality rate reported for myocardial infarction in the young.[6] The 4 percent incidence rate of perioperative myocardial infarction was also lower than the 14.7 percent rate reported from this institution in an age-unrestricted series of patients.[20]

The overall graft patency for all patients studied with cardiac catheterization was 85 percent, and there was no significant decrease in the graft patency rate at the 6 month, 1 and 3 year follow-up periods. The number of grafts studied at 5 years is too small to be significant. The internal mammary artery grafts had a higher patency rate than the vein grafts, with 97 percent patent at 6 months and 96 percent patent at 1 year. The improved patency for the internal mammary artery versus vein grafts is similar to that reported by Green[21] and by Loop et al.,[22] although in our series the difference was not statistically significant. In view of the importance of long-term patency in these young patients, we favor the internal mammary artery as the graft of choice for the left anterior descending coronary artery. The patency rate for vein grafts was similar to that reported by others. Grondin et al.[23] reported occlusion rates of 11.3 percent at 2 weeks, 20.4 percent at 1 year and 5.1 percent at 3 years. There was progression in the proximal obstructive lesions in the vessels grafted, as reported by others.[24] The number of totally obstructed vessels increased from 18 to 41, thus increasing their dependence

on the graft. In this group of young patients, therefore, long-term vein graft and internal mammary artery graft patency is critical.

The late mortality rate was 4 percent, with a mean follow-up period of 26 months. Two of the three deaths were presumed to be caused by a cardiac event; one patient died from unrelated renal failure. This would give a predicted 5 year mortality rate of 8 percent, or 1.6 percent/year. There are insufficient reported data to compare medically and surgically treated patients in this age group. However, our late mortality rate does compare favorably with the 22.7 percent rate reported in a series of young patients with myocardial infarction followed up for 10 years[6] although those patients were older than ours. The overall 4 year survival rate assessed from life table methods was 89 percent in a series of 532 age-unrestricted patients undergoing coronary revascularization[25] and 85.9 percent up to 60 months in 2,676 patients reported on by Reul et al.[18] The long-term prognosis for our group of young patients thus appears to be similar to that of the overall group of patients undergoing bypass surgery.

Relief of angina was similar to that reported by others,[25–27] and there was some decrease in the number of patients free of angina with time. Twenty-nine percent remained unemployed. This is disappointing in light of the 91 percent who returned to work after a myocardial infarction as reported by Kellerman[28] and 83 percent after revascularization in the series reported by Rimm et al.[29] This difference is possibly due to the large number of patients in our series who were engaged in heavy physical work, such as construction work and farming (44 percent), as opposed to sedentary occupations (13 percent). Rimm et al.[29] showed that the rate of return to work was lower for groups in occupations with large physical demands.

Implications: Our study thus shows that coronary revascularization can be performed at a reduced risk in younger patients. Despite the wide prevalence of predisposing factors, graft patency and the long-term prognosis are similar to those of other patients undergoing revascularization. Because of the importance of employment to young patients and their ability to lead a vigorous life, coronary revascularization has a special application for this group.

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Management of Hypercholesterolemia: Evaluation of Practical Clinical Approaches in Healthy Young Adults

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A work site-located clinic screened 6,000 employees (91 percent participation) and identified 146 hypercholesterolemic subjects (100 percent initial participation, 12 percent subsequent dropout rate). The subjects, aged 20 to 50 years, were randomly classified into four groups: Group A, treatment in a lipid intervention clinic with diet for 6 weeks, then diet plus clofibrate for the subsequent 18 weeks; Group B, diet treatment from a clinic nutritionist with the cooperation of the subject's private physician; Group C, referral for treatment by a private physician; and Group D, no intervention.

Initial mean cholesterol was 294 mg/100 ml. At 24 weeks, all intervention groups had decreases in serum cholesterol (Group A, 12 percent; Group B, 15 percent; Group C, 17 percent; $P < 0.001$). The control group (D) had a small decrease in cholesterol (4 percent). Decreases in cholesterol were correlated with weight loss and decrease in fasting serum triglycerides but not with the use of clofibrate. Serum cholesterol can be reduced in healthy young adults by several practical methods.

An association between serum cholesterol level and atherosclerotic cardiovascular disease has been recognized in epidemiologic, laboratory experimental and clinical investigations.[1–4] On the basis of these studies many experts currently recommend that persons with increased serum cholesterol be identified and treated.[5]

It is likely that maximal effect in decreasing risk of atherosclerotic disease related to hypercholesterolemia may be accomplished by defining a healthy young population with this hyperlipidemia and providing specific dietary and perhaps drug therapy.[2,6] However, previous experience in managing healthy young adults with an asymptomatic risk indicator provokes concern about patients' adherence to treatment.[7] Assuming the desirability of lowering cholesterol levels, this investigation was designed to determine how a sizable healthy working population with hypercholesterolemia can be most effectively identified and treated.

Methods

Selection of Subjects

The study was conducted as a part of the heart disease prevention program of the U.S. Public Health Service Hospital and Employee Health Service at the Social Security Administration headquarters, Baltimore, Maryland. The Social Security Administration is a governmental organization staffed by an administrative and clerical work force. Over a 2 year period, approximately 6,000 employees participated in a cardiovascular screening program that included fasting serum lipid determination, electrocardiogram, chest radiograph, blood pressure measurement and a self-administered health-status questionnaire.

Screening process: The program was explained by a program physician in orientation meetings to groups of about 200 employees selected by department and organized by a worker from that department. This approach, plus a media campaign with pamphlets and posters, resulted in a voluntary participation rate

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of 91 percent of eligible employees. Details of this screening program are presented elsewhere.[8] Participants having triglyceride or cholesterol measurement in the top 5 percent by age decade were recalled for repeat fasting lipid measurement. The response rate for those recalled was 98 percent. The importance of a true 14 hour fast (except for water and medication) and maintenance of normal diet pattern was emphasized. If serum cholesterol on the second determination exceeded arbitrary age-related limits (age 20 to 29 years, 240 mg/100 ml or more; age 30 to 39, 270 mg/100 ml or more; age 40 to 49, 310 mg/100 ml or more[9]), paper electrophoresis lipoprotein typing was performed by the method of Lees and Hatch.[10] Lipoprotein types were classified by criteria described elsewhere.[8,11]

Subjects: One hundred fifty-two subjects aged 20 through 50 years were identified from the two-stage screening process having type II (IIa or IIb) hyperlipoproteinemia. Screened subjects with other types of hyperlipoproteinemia, on special diets (such as vegetarian or high protein), with normal cholesterol at the second screening or historical evidence of cardiovascular disease were excluded and entered in other study protocols or referred to their private physicians for appropriate treatment, or both. To rule out secondary hyperlipoproteinemia, the 152 initially accepted subjects were recalled for a medical history, physical examination and specialized laboratory testing including urinalysis, serum SMA-12 chemistry determinations, serum thyroxine level measurements and serum protein electrophoresis. Six of the 152 were then excluded for presumed secondary hyperlipidemia. Our inclusion criteria were liberal because we intended to study the large majority of instances of type II hyperlipidemia in a "normal" working population. Subjects with obesity, mild hypertension, a moderate consumption of alcohol and those taking birth control pills, conjugated estrogens or antihypertensive drugs were included. Also included but not separately classified were subjects with familial type II hyperlipidemia. The number of these subjects was probably small because this disorder has a low estimated prevalence rate in the general population (0.1 to 0.2 percent).[12]

Intervention Protocol

After appropriate explanation, all 146 eligible subjects volunteered to participate in this 24 week intervention study. Informed consent was obtained from both the subjects and their physicians. They were then randomly assigned (without stratification) to one of four study groups, A, B, C or D (Table I).

Group A: These 37 subjects were treated at a Lipid Intervention Clinic conveniently located at their site of employment and staffed by one nutritionist and one physician. With the approval of the subject's private physician, all treatment of the type II lipid abnormality was handled at this clinic. Subjects were given easy access to the clinic nutritionist and encouraged to use his services. Throughout the study we emphasized nutritional education to change dietary habits; only after 6 weeks of dietary treatment was drug therapy (clofibrate) added.

Dietary plans were consistent with the recommended nutritional prescription for type II hyperlipoproteinemia[13]: (1) restriction of dietary cholesterol, (2) restriction of saturated fat, and (3) increased intake of polyunsaturated fat. Subjects were instructed to limit total meat consumption, and intake of beef, lamb, ham or pork was restricted to 3 ounces three times a week. Polyunsaturated vegetable fats were recommended for cooking and table use. Consumption of egg yolks, whole milk and cheese, cream products and baked goods was discouraged. Weight reduction was not stressed although counseling was given if the subject requested it.

TABLE I

Treatment in the Four Subgroups

Group	Intervention	
	Diet	Drug
A	Lipid clinic	Lipid clinic
B	Lipid clinic	Private physician
C	Private physician	Private physician
D	None	None

Repeat measurements were made of fasting serum triglyceride and cholesterol levels at 6, 12 and 24 weeks. The subjects were told their lipid levels to encourage program adherence. The nutritionist conducted group instruction and discussion meetings for all Group A participants at the start of dietary intervention. The nutritionist also held individual meetings with participants every 2 to 3 weeks throughout the study but more frequently in the initial weeks. The wives of about half of the married men attended at least one individual or group session.

After the initial 6 weeks of dietary intervention, the subjects were given clofibrate (chlorophenoxyisobutyric acid, Atromid-S),[14] 500 mg orally four times a day, and instructed to continue this medication for the remaining 18 weeks of the study. They were carefully told that this medication was not a substitute for dietary treatment and that continued conscientious nutritional management was essential. At 24 weeks the study was terminated and each subject was referred to his private physician, who was given the results of all lipid measurements and appropriate recommendations for continued care.

Group B: These 37 subjects received the same counseling of the clinic nutritionist as described for Group A, but access to the clinic physician was limited to the initial visit. Subjects were encouraged to visit their private physician for drug or other management. The private physicians were given their patients' initial blood chemistry values and data on the treatment of type II hyperlipidemia[13,15] and asked to follow the study protocol (6 weeks of diet therapy supplemented with orally adminstered clofibrate, 500 mg four times a day from the 6th to 24th weeks). Fasting cholesterol and triglyceride measurements were taken at 6, 12 and 24 weeks and these results given to the participant and his private physician.

Group C: All of these 38 subjects were referred to their private physician for treatment. Each physician was mailed the participant's lipid values, normal range according to the study, a description of the 24 week project and appropriate information[13,15] about dietary and drug management of type II hyperlipoproteinemia. The intention was that treatment would be as similar as possible to that of Group A and B subjects for all 24 weeks of the study, with administration of clofibrate, 500 mg orally four times a day from the 6th to the 24th weeks. Fasting triglyceride and cholesterol measurements were also made in Group C subjects at 6, 12 and 24 weeks, and these results were forwarded to the private physicians.

Group D: These 34 "control" subjects were told that initial tests had revealed elevated serum lipid levels and that these levels would be monitored. Repeat fasting triglyceride and cholesterol measurements were performed at a follow-up visit in the 24th week of the study, after which these subjects were also referred to their private physician with appropriate information and recommendations.

TABLE II

Demographic Characteristics and Mean Values (± standard error of the mean)

Group	Subjects* (no.)	Age (yr)	Sex		Weight (kg)	Relative Weight	Lipid Type		Baseline Values (mg/100 ml)	
			Male	Female			IIa	IIb	Cholesterol	Triglyceride
A	37 (31)	31.3 ± 1.4	19	18	72.7 ± 3.2	1.09 ± 0.03	23	14	291 ± 7	133 ± 12
B	37 (29)	31.6 ± 1.2	22	15	72.5 ± 1.7	1.07 ± 0.02	23	14	295 ± 7	147 ± 14
C	38 (34)	34.9 ± 1.6	19	19	77.3 ± 2.9	1.14 ± 0.03	23	15	299 ± 6	137 ± 11
D	34 (34)	33.4 ± 1.5	20	14	74.7 ± 2.9	1.15 ± 0.04	19	15	292 ± 7	140 ± 7

* Numbers in parentheses indicate subjects completing study.
Differences among groups are not significantly different ($P > 0.05$) for any characteristic.

Laboratory Methods

Blood was drawn by venipuncture in 10 cc evacuated tubes after a 12 to 14 hour fast. Total cholesterol and triglyceride levels were determined with a Technicon Autoanalyzer II by methods described elsewhere.[16,17] All specimens were observed overnight for presence of a cream layer in the serum indicating chylomicrons. Lipoprotein electrophoresis was performed on paper as described elsewhere.[17] The serum of patients with elevation of both triglyceride and cholesterol levels were subjected to ultracentrifugation and paper electrophoresis of the fractions to identify and exclude from this study patients with type III hyperlipidemia.

Laboratory accuracy (validity and reproducibility) for triglyceride and cholesterol measurement was maintained by cooperation with the Center for Disease Control (CDC) Cooperative Lipid Standardization program. Our lipid laboratory was classified as "standardized" by this project. Coded serum samples were analyzed on the same and different days throughout the study. Duplicates analyzed on the same day demonstrated a standard deviation of random measurement error of 5.1 mg/100 ml for cholesterol and 7.0 mg/100 ml for triglycerides; on different days 6.6 mg/100 ml for cholesterol and 4.8 mg/100 ml for triglycerides.

Results

Group characteristics and adherence to the protocols: Table II lists the characteristics of the 146 patients studied. The four groups (A, B, C and D) did

TABLE III

Mean (± standard error of the mean) Fasting Serum Triglyceride and Cholesterol Levels and Relative Body Weights

	Group A	Group B	Group C	Group D
Subjects (no.)	31	29	34	34
Baseline values				
Relative weight	1.10 ± 0.04	1.07 ± 0.02	1.16 ± 0.04	1.15 ± 0.04
Cholesterol (mg/100 ml)	291 ± 7	296 ± 9	299 ± 6	292 ± 7
Triglycerides (mg/100 ml)	137 ± 14	145 ± 16	138 ± 13	140 ± 13
Values at 6 weeks				
Relative weight	1.07 ± 0.03 (−3%) $P < 0.001$	1.05 ± 0.02 (−2%) $P < 0.001$	1.12 ± 0.03 (−3%) $P < 0.001$	. . .
Cholesterol (mg/100 ml)	252 ± 9 (−13%) $P < 0.001$	268 ± 8 (−9%) $P < 0.001$	267 ± 7 (−11%) $P < 0.001$	. . .
Triglycerides (mg/100 ml)	119 ± 10 (−13%) NS	120 ± 11 (−17%) $P < 0.05$	130 ± 12 (−6%) NS	. . .
Values at 12 weeks*				
Cholesterol (mg/100 ml)	237 ± 10 (−19%) $P < 0.001$	252 ± 8 (−15%) $P < 0.001$	260 ± 7 (−14%) $P < 0.001$	. . .
Triglycerides (mg/100 ml)	93 ± 9 (−32%) $P < 0.005$	108 ± 13 (−26%) $P < 0.001$	99 ± 7 (−29%) $P < 0.001$	. . .
Values at 24 weeks				
Relative weight	1.07 ± 0.03 (−3%) $P < 0.005$	1.04 ± 0.02 (−3%) $P < 0.005$	1.13 ± 0.04 (−3%) $P < 0.05$	1.14 ± 0.04 (−1%) NS
Cholesterol (mg/100 ml)	256 ± 11 (−12%) $P < 0.001$	252 ± 9 (−15%) $P < 0.001$	251 ± 8 (−16%) $P < 0.001$	280 ± 7 (−4%) $P < 0.05$
Triglycerides (mg/100 ml)	108 ± 11 (−21%) $P < 0.05$	106 ± 14 (−27%) $P < 0.005$	106 ± 11 (−23%) $P < 0.005$	125 ± 12 (−10%) $P < 0.05$

* Weights not measured at 12 week examination.
Figures in parentheses indicate percent changes from baseline. P (probability) value (paired ± test) compares baseline with subsequent values. NS = not significant.

not differ significantly at the start of the study in age, sex distribution, race (20 to 30 percent black), body weight, lipid type distribution, cigarette smoking history (40 to 50 percent), cholesterol level or triglyceride level. The subjects were representative of the Social Security Administration work force in that they were predominantly clerical or white collar in job classification and rarely supervisory, executive or blue collar. Relative weights were calculated by the ratio of the patient's weight to that recommended by the National Research Council after correction for height.[18] Baseline cholesterol and triglyceride levels presented (Tables II and III) were those observed at the second screening venipuncture. During the 24 weeks of the trial 18 subjects (6 in Group A, 8 in Group B and 4 in Group C; 16 percent of intervention subjects) left the study, either refusing to continue or becoming unavailable for follow-up contact. The major reasons for leaving the study included termination of employment, difficulty adhering to diet or drugs or discouragement over lack of reduction of cholesterol level despite diet change. The baseline characteristics of the nine men and nine women who left the study did not differ significantly from those of subjects who completed the study. All other participants fulfilled all scheduled appointments; 26 of 29 subjects in Group B and 32 of 34 in Group C visited their private physician. Their visit frequently occurred after repeated reminders by the clinic secretary. During the study only 4 Group B and 4 Group C subjects reported receiving clofibrate prescriptions from their private physician, but 32 Group C subjects reported receiving a diet from their private physician. Administration of clofibrate according to the protocol was discontinued in three subjects in Group A because of the reported development of nausea, leg cramps or impotence. White blood cell counts and serum creatine phosphokinase levels in these and all other subjects in Groups A, B and C taking clofibrate disclosed no evidence of drug toxicity. Drug adherence was monitored in Group A subjects by historical evaluation, pill counts and records of refilled prescriptions.

TABLE IV

Decrease or Increase in Cholesterol at 24 Weeks

Group	Subjects (no.)	
	Increased	Decreased
A	4	27
B	4	25
C	3	31
D	12	22

Cholesterol and triglyceride levels: Table III gives the average fasting serum triglyceride and cholesterol values and body weight measurements for each of the four groups at the start of the study (second screening value) and at 6, 12 and 24 weeks. Table IV shows the number of subjects whose cholesterol level increased or decreased at 24 weeks.

Cholesterol level declined during the study for all experimental groups (Fig. 1). Subjects in Group A, managed entirely by the Lipid Intervention Clinic,

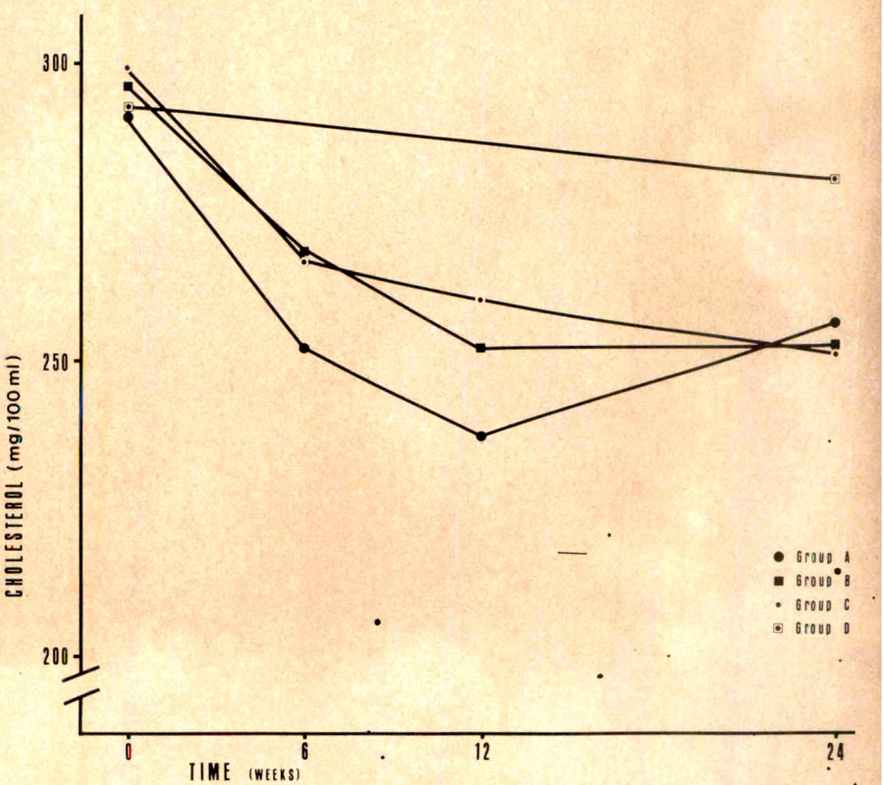

FIGURE 1. Mean serum cholesterol (mg/100 ml) for Groups A, B, C and D during the 24 week study.

TABLE V

Multiple Regression Analysis

Variable	Regression Coefficient	Standardized Regression Coefficient	Adjusted *t*
ΔTri (mg/dl)	0.340	19.4	+5.27
ΔRel Wt	254	13.1	+3.27
ΔTri × Rel Wt (mg/dl)	2.33	10.0	+2.18

ΔChol = 0.34 (ΔTri) + 254 (ΔRel Wt) + 2.33 (ΔTri × ΔRel Wt) − 21.5 no. = 128
Multiple correlation coefficient = 0.494

ΔChol = cholesterol (mg/100 ml) at 24 weeks − baseline cholesterol.

ΔTri = triglycerides (mg/100 ml) at 24 weeks − baseline triglycerides.

ΔRel Wt = relative weight at 24 weeks − baseline relative weight where relative weight = actual weight/ideal weight.

demonstrated the largest decrease at 6 weeks (13 percent) and 12 weeks (19 percent). But at 24 weeks, the mean cholesterol of this group had risen again to a level similar to that in other intervention groups (B and C). Group B (clinic nutritionist and private physician) and Group C (private physician management) had a decrease in cholesterol throughout the 24 weeks of the study. At 24 weeks, Groups B and C had decreases of 15 percent and 16 percent, respectively, in cholesterol. Group D ("control") also demonstrated a small but significant (4 percent, $P < 0.05$) decrease in cholesterol at 24 weeks.

Triglyceride levels declined for all experimental groups during the study (Fig. 2). All intervention groups (A, B and C) had similar decreases in triglyceride level at 6 and 12 weeks. At 24 weeks the values stabilized at significant decreases for each group (A, 21 percent; B, 27 percent; C, 23 percent; and D, 10 percent).

Baseline cholesterol levels for men and women did not differ significantly. However, within the intervention groups (A, B and C), women experienced somewhat larger reductions in cholesterol than men (16.6 versus 12.0 percent). Serum triglyceride levels at the baseline study were significantly higher in men than in women, a finding that concurs with survey data.[8] Although the absolute reduction in triglycerides in the intervention groups was similar, the lower baseline levels made the percent reduction in women slightly larger (28 versus 20 percent). These differences were not statistically significant.

The relation of cholesterol change between the baseline study and 24 weeks and the other variables was examined by multiple regression analysis (Table V). This revealed a statistically significant relation between change in cholesterol and change in triglycerides and relative weight. Change in cholesterol was not related to age, sex or lipid type (IIa or IIb) in this analysis.

Discussion

Although it is established that serum cholesterol levels can be decreased in hospitalized patients and

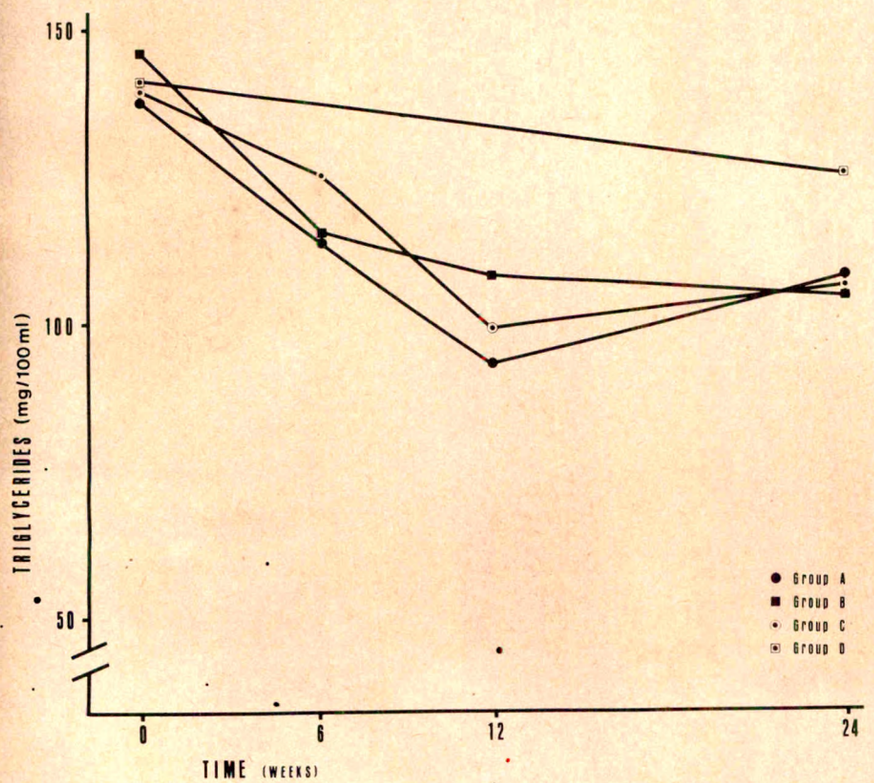

FIGURE 2. Mean fasting serum triglycerides (mg/100 ml) for Groups A, B, C and D groups during the 24 week study.

volunteer groups, there is a need to learn how this can be most effectively and economically accomplished among unselected persons in their usual environment. Because the major burden of hypercholesterolemia in the United States is probably diet-induced, methods of diet modification, as used here, are most likely to be effective in lowering cholesterol levels. The development of atherosclerotic disease seems to be a lifelong process and implies the identification and motivation of large numbers of relatively young persons at higher risk but asymptomatic to adhere to long-term diet modification and possibly drug therapy.

Because most young and middle-aged adults are employed, the work site is a convenient place for conducting medical screening and intervention programs. A high participation rate for screening, initial enrollment and adherence to program activities was attained in our study. The convenience and practicality of attending a work site lipid clinic during work hours (at no loss in pay) clearly contributed to the excellent participation. The educational program on the heart, group meetings and scheduling by representatives from within screened departments may also have contributed.

Diet intervention and serum cholesterol: Considerable information exists regarding diet intervention trials to lower cholesterol in people with established atherosclerotic disease and in healthy selected populations. Cholesterol decreases of 11 to 22 percent from baseline value have been observed with the largest reductions occurring in groups with established atherosclerotic disease. Serum cholesterol levels decreased in all groups participating in our study. The magnitude of decrease observed in the intervention groups (A, 12 percent; B, 15 percent; C, 16 percent) at 24 weeks is similar to that observed in other trials. However, the similarity of cholesterol decreases among our three intervention groups was unexpected. We had predicted from prior experience that Group A and B subjects managed by the lipid clinic would demonstrate the largest decreases in serum cholesterol because they received considerable face to face instruction, free medication (Group A) and frequent consultation with the clinic staff. Earlier experience of that staff with healthy subjects having type IV hyperlipoproteinemia demonstrated the largest declines in lipid levels in those subjects with intensive clinic management.[19]

Possible explanations of this relatively good management by private physicians (or deficiency of the clinic intervention) should be considered. In subjects assigned to Group C (managed by private physician), extensive efforts were made by the clinic secretary and staff physician to ensure that the subject visited the physician. This effort was clearly successful and 32 of 34 subjects had physician office visits and received diet instructions. Repeated visits to the clinic for venipuncture and revelation of their lipid levels probably reinforced cholesterol-lowering diet changes in Group C subjects. Group A subjects received clofibrate at 6 weeks after a uniform and excellent response (13 percent reduction) to diet alone. At 12 weeks they had a further 6 percent reduction to 19 percent. But at 24 weeks the cholesterol level had risen again. Despite educational efforts many Group A subjects stated that diet adherence was no longer important if they had a pill. In contrast, in subjects in Group B, who were given diet alone under the guidance of the clinic staff, cholesterol decreases were maintained. In this study clofibrate appeared ineffective in additionally lowering serum cholesterol levels. Finally, the magnitude of cholesterol reduction (10 to 20 percent) observed in the dietary period of this and other studies may represent the limit of potential lipid lowering from prescribed diets. Larger decreases may depend on new diet, drug therapy regimes, or both.

Group D (the "control" group) had small but significant decreases in cholesterol (4 percent). This decrease is partly attributed to inevitable communication among groups (which we attempted to minimize) and the phenomenon of regression toward the mean with repeat sampling, which occurs in any population first selected because of increased risk indicators.

Relation between cholesterol and triglyceride levels and weight reduction: Although weight reduction and decrease in serum triglycerides were not goals of this study, both occurred in all intervention groups and were statistically related to changes in cholesterol. This protocol was not designed to separate the relative effects of weight reduction versus change in dietary composition. It is likely that each plays an independent role in cholesterol reduction. Serum cholesterol levels have previously been observed to fall with reduction in serum triglycerides.[19,20] This reduction may be related to alterations in the levels of the common carrier modalities for lipids (low density lipiproteins [LDL], very low density lipoproteins [VLDL] and high density lipoproteins [HDL]) or other factors as yet unperceived.

Implications: At this time "definitive" (Lipid Research Centers, Multiple Risk Factor Intervention Trial) studies are in progress that are designed to establish whether lowering serum cholesterol levels in subjects with type II hyperlipoproteinemia results in a decrease in atherosclerotic complications. However, our study indicates that most type II hyperlipoproteinemic subjects in a working population can be identified and effectively treated. This study also indicates that specific treatment by lipid clinic or by private physician can effectively decrease fasting cholesterol levels in apparently healthy subjects, aged 20 to 50 years, for a period of at least 24 weeks.

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Echocardiographic Features of Total Anomalous Pulmonary Venous Connection to the Coronary Sinus

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Six infants with anomalous connection of the pulmonary veins to the coronary sinus were studied with single crystal echocardiography. The posterior left atrial wall echo was identified by its continuity with the left ventricular posterior wall echo during a sweep from the left atrium to the left ventricle. In five of the six infants an echo-free space measuring 7 to 9 mm was identified behind the posterior left atrial wall; this space was thought to represent the common pulmonary vein. In four of these five, and also in the remaining infant, a highly mobile linear echo with a double wave form per cardiac cycle was recorded behind the posterior aortic wall and anterior mitral leaflet echoes. Echocardiographic contrast studies after the injection of saline solution into the coronary sinus disclosed that this additional echo was produced by the anterior wall of the coronary sinus.

The anatomic connections of the pulmonary veins were established in each patient with pulmonary cineangiography. In four of the six patients all four pulmonary veins were connected to the coronary sinus by way of a common pulmonary vein; in the remaining two patients three of four pulmonary veins were connected to the coronary sinus, while the left upper lobe pulmonary vein was connected to the left innominate vein. The coronary sinus was greatly enlarged in each patient.

Total anomalous pulmonary venous connection may be identified echocardiographically by the presence of a well defined echo-free space behind the left atrium together with echocardiographic features of right ventricular volume overload.[1,2] The normal coronary sinus cannot be seen echocardiographically. Gramiak[3] could identify an enlarged coronary sinus in one patient with persistent connection of the left superior vena cava to the coronary sinus and in a patient with total pulmonary venous connection to the coronary sinus. In this report we describe the echocardiographic features of six infants with total or near total anomalous pulmonary venous connection to the coronary sinus.

Material and Methods

Single crystal echocardiography was performed before cardiac catheterization in six infants aged 1 to 7 months using an Ekoline or Rohe machine. The left atrial posterior wall-pericardial echo was identified by its continuity with the left ventricular posterior wall-pericardial echo on a sweep from the left atrium to the left ventricle. Gain settings were varied in order to identify an echo-free space behind the left atrium. In one patient (Case 2) an echocardiographic contrast study was recorded after injection of saline solution into the coronary sinus.

Cardiac catheterization was performed in each case, and the exact connections of the pulmonary veins were established with pulmonary cineangiography.

Observations

Echocardiography: The echocardiographic measurements of each infant are recorded in Table I. An echo-free space, measuring 7 to 9 mm in internal

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diameter, was identified behind the left atrial posterior wall echo in Cases 1 to 5 (Fig. 1 and 2). This space was consistent and did not extend behind the left ventricular posterior wall echo; we think it represents the chamber formed by the confluence of the pulmonary veins. In one infant (Case 6) no echo-free space was recorded behind the left atrium.

In five of the six infants (Cases 1 to 4 and Case 6) an abnormal linear echo was consistently recorded behind the posterior aortic wall and anterior mitral leaflet echoes. In one patient (Fig. 3) this additional echo was confined largely to the atrioventricular (A-V) junction, but in the other patients it was recorded even with the transducer angled toward the superior part of the left atrium (Fig. 1 and 4). This linear echo was characterized by a double wave-like motion per cardiac cycle (Fig. 5) that corresponded closely with the simultaneous pressure wave form recorded in two patients with the catheter positioned in the coronary sinus or left atrium.

Echocardiographic contrast study: In one case (Case 2) an echocardiographic contrast study was recorded after the injection of saline solution into the coronary sinus (Fig. 6). The echoes produced by the saline injection appeared first behind the mobile linear echo representing the anterior wall of the coronary sinus. The echoes subsequently appeared in the left atrium, the right ventricle and, finally, the aorta. During one echocardiographic contrast study, after the injection of a larger amount of saline solution, the echoes also appeared in the posterior echo-free space thought to represent the common pulmonary vein (Fig. 6C). However, before this occurred there was a delay of about 1 second that could be accounted for only if the bubbles produced by the saline injection passed

TABLE I

Echocardiographic Measurements

Case no.	Age (mo)	BSA (m^2)	Ao (mm)	LA (mm)	PA (mm)	RVPEP/RVET	RVAW (mm)	$RVID_d$ (mm)	S (mm)	$LVID_d$ (mm)	LVPW (mm)	CPV (mm)	PA Pressure (mm Hg)
1	3	0.23	9	7	. . .	. . .	4	18	5	10	3	7	. . .
2	1	0.20	11	11	16	0.41	6	16	5	15	3	7	44/31 (31)
3	1	0.23	11	5	17	0.29	7	19	5	13	3	7	52/25 (37)
4	3	0.26	10	8	. . .	0.43	5	16	5	13	4	8	40/18 (24)
5	3	0.32	13	10	19	0.39	6	19	4	20	4	9	38/18 (27)
6	7	0.34	13	6	20	0.32	6	17	4.5	15	3.5	. . .	68/30 (50)

Figures in parentheses indicate mean pressure.
Ao = aorta; BSA = body surface area; CPV = common pulmonary vein (internal diameter); LA = left atrium; $LVID_d$ = left ventricular diastolic diameter; LVPW = left ventricular posterior wall; PA = pulmonary artery; RVAW = right ventricular anterior wall; RVET = right ventricular ejection time; $RVID_d$ = right ventricular diastolic diameter; RVPEP = right ventricular preejection period; S = septum.

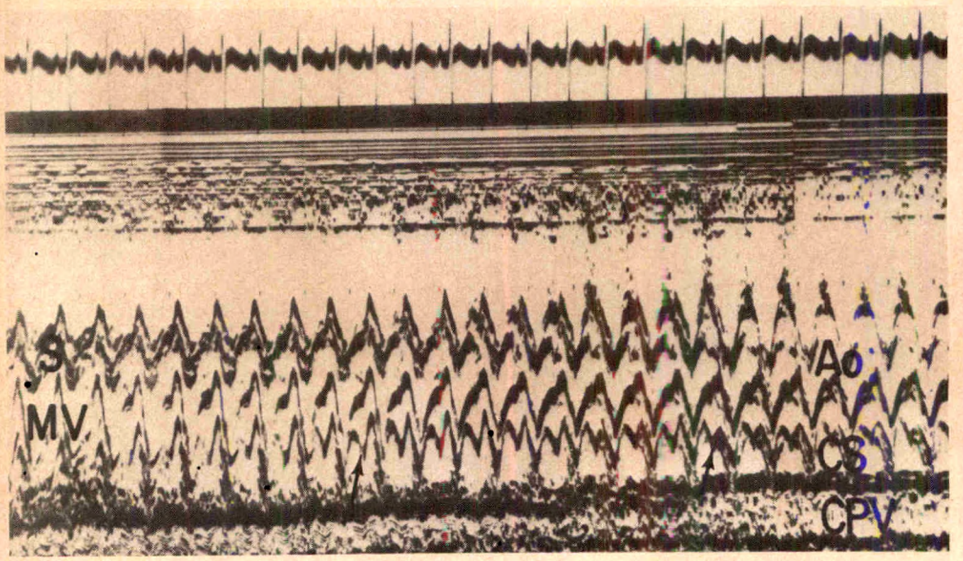


FIGURE 1. Case 1. Echocardiogram showing sweep from the aorta (Ao) down to the mitral valve (MV) and ventricular septum (S). The common pulmonary vein (CPV) is recorded as an echo-free space behind the dense pericardial echo in the region of the left atrium. An additional very mobile linear echo **(arrows)** with a double wave form was recorded behind the posterior aortic wall and extends behind the mitral valve. This echo represents the anterior wall of the coronary sinus (CS).

through the pulmonary circulation. This delay may represent some form of pulmonary arteriovenous shunting that kept the bubbles from being trapped in the pulmonary capillaries.

Right ventricular dimensions: All six patients had echocardiographic features suggesting pressure and volume overload of the right ventricle with an increase in the right ventricular anterior wall and ventricular septal thickness as well as an increase in the right ventricular diastolic diameter and paradoxical motion of the ventricular septum (Fig. 7). The preejection period to ejection time ratio for the right ventricle could be measured from the pulmonary valve echo in five of the six patients; this ratio was greater than 0.30 in four patients but normal in the remaining patient (Table I).

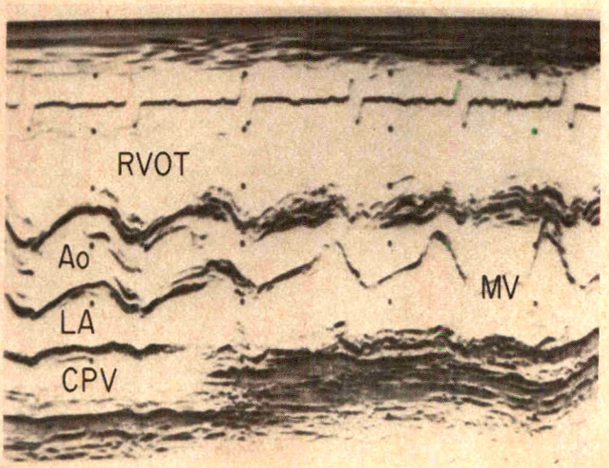


FIGURE 2. Case 5. Echocardiogram showing an echo-free space behind the left atrium (LA) representing the common pulmonary vein (CPV). Ao = aorta; MV = mitral valve; RVOT = right ventricular outflow tract.

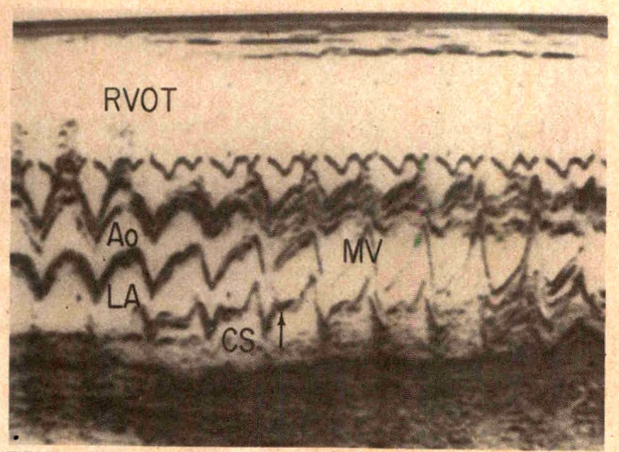


FIGURE 4 (above). Case 4. Echocardiogram showing sweep from the aorta (Ao) to the mitral valve (MV). **Arrow** marks mobile echo produced by the anterior wall of the coronary sinus (CS). LA = left atrium; RVOT = right ventricular outflow tract.

FIGURE 5 (right). Case 1. Echocardiogram illustrating double wave form of a linear echo **(arrow)** from the anterior wall of the coronary sinus (CS). Ao = aorta; PV = pulmonary vein.

Cardiac catheterization: All six infants had a marked increase in oxygen saturation at the atrial level and mild systemic desaturation. Each had mild or moderate pulmonary hypertension. Pulmonary cineangiography disclosed total anomalous pulmonary venous connection. In four of the six infants (Cases 2 through 5) each of the pulmonary veins entered the coronary sinus by way of a common pulmonary ve-

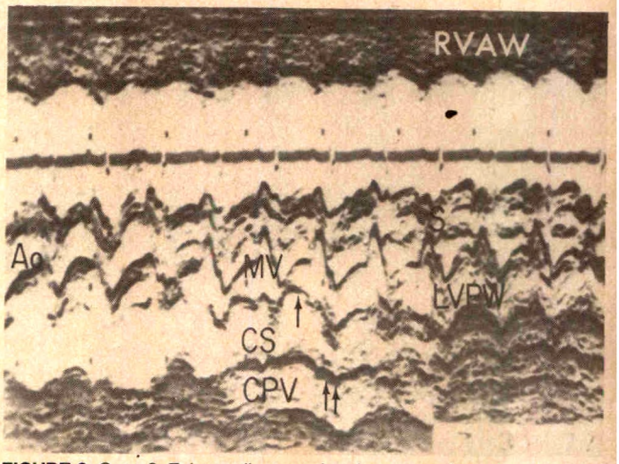
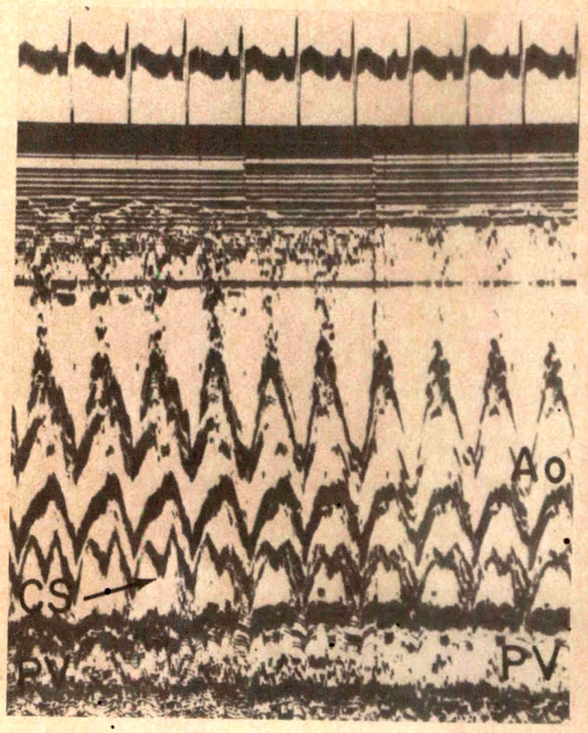
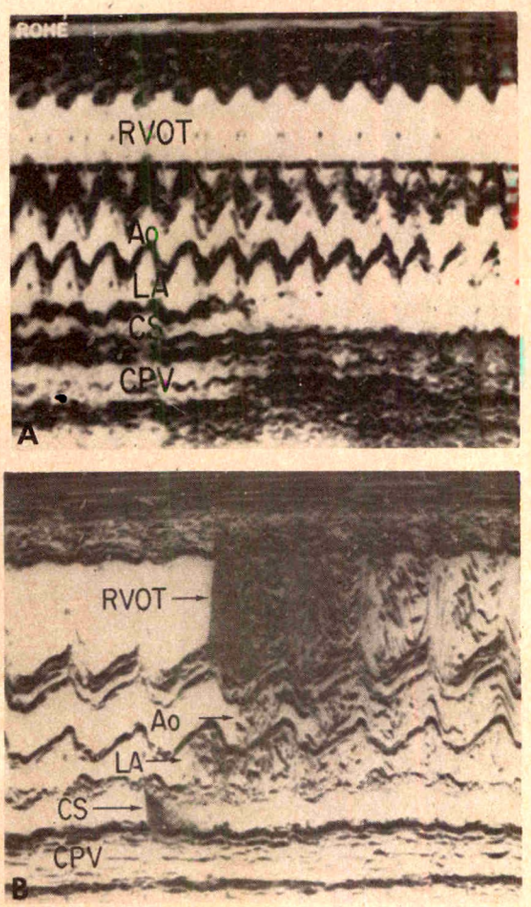


FIGURE 3. Case 3. Echocardiogram showing sweep from the aorta (Ao) to the left ventricle. Both the coronary sinus (CS) and the common pulmonary vein (CPV) are recorded. The **single arrow** points to the anterior wall of the coronary sinus. The **double arrow** points to the pericardial-left atrial posterior wall echo. LVPW = left ventricular posterior wall; MV = mitral valve; RVAW = right ventricular anterior wall; S = septum.





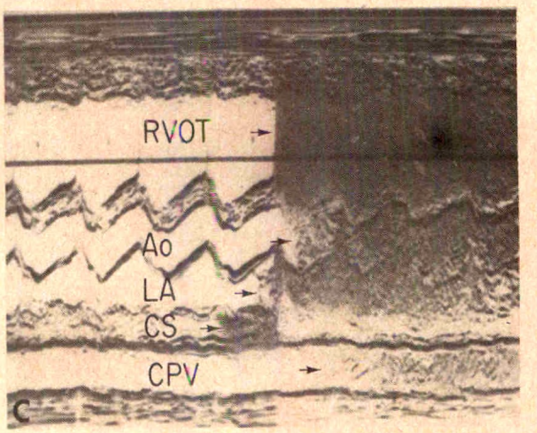


FIGURE 6. Case 2. **A**, echocardiogram showing a linear echo from the anterior wall of the coronary sinus (CS) and an echo-free space behind the pericardium representing the common pulmonary vein (CPV). **B**, echocardiogram recorded after injection of saline solution into the coronary sinus. Additional echoes appear first in the coronary sinus, then in the left atrium (LA) and right ventricular outflow tract (RVOT) and, finally, in the aorta (Ao). **C**, echocardiogram recorded after the injection of an increased amount of saline solution into the coronary sinus. The echoes from the saline injection appear in an order similar to that seen in **B** except that they appear late (after a delay of about 1 second) in a posterior echo-free space representing the common pulmonary vein.

nous channel. In Cases 1 and 6 the left upper lobe pulmonary vein was connected to the left innominate vein, and the other three pulmonary veins were connected to the coronary sinus. The coronary sinus was greatly enlarged in each patient. In Case 5 the coronary sinus was oriented in a more vertical direction than usual, which may account for our failure to record the coronary sinus by echocardiography in that case.

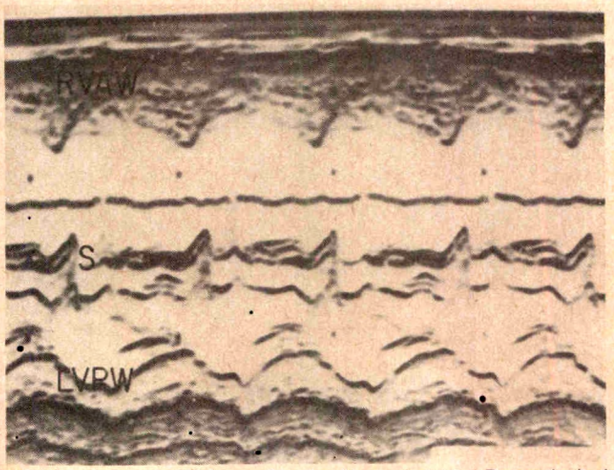


FIGURE 7. Case 3. Echocardiogram illustrating type B paradoxical motion of the ventricular septum (S), increased right ventricular diameter and increased right ventricular anterior wall thickness (RVAW). LVPW = left ventricular posterior wall.

Discussion

The coronary sinus is situated in the A-V groove on the posterior surface of the heart. It is covered by spiraling muscle fibers from the left atrial wall as well as by pericardium[4,5] and thus is partially incorporated into the posterior left atrial wall. The coronary sinus may become greatly enlarged because of increased blood flow when anomalous pulmonary veins are connected to it. In such cases it is often larger than the left atrium[6] and may resemble a third atrial chamber.

Coronary sinus echo: Gramiak[3] documented the echocardiographic finding of an additional linear echo behind the mitral valve in one case of persistent connection of the left superior vena cava to the coronary sinus and also in a case with total anomalous pulmonary venous connection to the coronary sinus. In our patients with this malformation, we found that this additional linear echo was easily recorded and had a characteristic double wave-like motion per cardiac cycle. This echo can be recorded behind the anterior mitral leaflet echo (in the A-V junction); it extends for a variable distance even into the upper portions of the left atrium and is recorded behind the posterior aortic wall echo. This linear echo represents the anterior wall of the coronary sinus as demonstrated with echocardiographic contrast studies after saline injection into the coronary sinus. The posterior wall of the coronary sinus is recorded in

conjunction with the left atrial wall-pericardial echo, which is in continuity with the pericardial echo behind the left ventricle. In contrast to the linear echo produced by the anterior wall of the coronary sinus, the echo from the posterior left atrial wall and pericardium does not exhibit a significant degree of motion.

Common pulmonary vein echo-free space: In most of our patients we recorded a large clear echo-free space behind the left atrial wall-pericardial echo. We think that this space represents the common pulmonary vein formed by the confluence of the anomalously connected pulmonary veins. It may be recorded in total anomalous pulmonary venous connection to sites other than the coronary sinus.[1]

Right ventricular overload: In addition to these two findings, each of our patients had echocardiographic features of pressure and volume overload of the right ventricle with increases in right ventricular anterior wall thickness and right ventricular diameter and paradoxical motion of the ventricular septum.

Diagnostic features: In the echocardiographic diagnosis of total anomalous pulmonary venous connection, one should recognize that the pulmonary veins do not always coalesce to form a large common pulmonary venous chamber and that, even if the veins do coalesce, the chamber may not be located behind the left atrium. In such cases no echo-free space can be recorded behind the left atrium. Some echocardiographers have reported false positive diagnoses on the basis of a relatively echo-free space behind the left atrium.[7,8] The diagnosis in our patients with anomalously connected pulmonary veins to the coronary sinus was based on the combined recording of the common pulmonary venous chamber as well as the identification of the coronary sinus.

Differential diagnosis: The coronary sinus may also be enlarged, but to a lesser degree, in other situations. Two examples in our experience have been persistent connection of the left superior vena cava to the coronary sinus and tricuspid insufficiency. In a few such cases we have been able to record the additional linear echo representing the anterior wall of the coronary sinus. However, in these cases the echo recorded exhibited less motion than the echo in the cases with anomalous pulmonary venous connection to the coronary sinus. Also, the echo was confined to the region of the A-V groove (mitral-aortic junction) and was not associated with the recording of an additional echo-free space behind the left atrium.

Other linear echoes have been recorded within the left atrium in patients with cor triatriatum or supravalve mitral stenosing ring and occasionally in normal patients.[9–13] In normal patients this linear echo is recorded with the transducer angled toward the superior portion of the left atrium. This echo exhibits little motion and therefore has not been difficult to differentiate from the echo produced by the anterior wall of the coronary sinus. In the reported cases with cor triatriatum, as well as in the one case we have seen, the additional linear echo was recorded within the left atrium in various positions, and its motion was usually parallel with the aortic root motion. We anticipate difficulty in distinguishing this echo from the coronary sinus echo although the double wave-like motion in the latter may be characteristic. There is insufficient documentation of the echocardiographic features of supravalve mitral stenosing ring[12,13] for us to feel confident in differentiating the echo it produces from the echo produced by the anterior wall of the coronary sinus.

Implications: Echocardiography proved useful in our patients in identifying the likelihood of anomalous pulmonary connection to the coronary sinus. Cardiac catheterization and angiography were planned with specific attention given to excluding other anomalies and establishing the exact connection of the individual pulmonary veins.

Acknowledgment

We express our appreciation to Cheryl Lawrence and Ellen Johnson for technical assistance, and to Tina Osborne for preparation of the manuscript and illustrations.

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Elective Mapping and Surgical Division of the Bundle of Kent In a Patient With Ebstein's Anomaly Who Required Tricuspid Valve Replacement

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A 14 year old girl with Ebstein's anomaly and Wolff-Parkinson-White syndrome without supraventricular tachycardia underwent closure of an atrial septal defect and tricuspid valve commissurotomy. Her postoperative course was complicated by her first episodes of recurrent debilitating paroxysmal supraventricular tachycardia. Severe tricuspid insufficiency with low cardiac output necessitated a repeat intracardiac operation. At reoperation the patient underwent successful tricuspid valve replacement with concomitant cardiac mapping and division of the bundle of Kent. In patients with heart disease requiring intracardiac repair who also have Wolff-Parkinson-White syndrome, elective surgical division of the anomalous bundle is recommended whether or not preoperative attacks of tachycardia have occurred.

The Wolff-Parkinson-White syndrome occurs in association with Ebstein's anomaly, its prevalence rate ranging from 5 to 25 percent in reported series.[1–4] In patients with these conditions, episodes of paroxysmal supraventricular tachycardia are common[1–4] and often easily controlled medically. However, patients with refractory tachycardia are faced with a life-threatening problem.[2,5–7] The availability of successful surgical techniques to divide anomalous pathways in such patients[5,8] raises the question: What are the indications for this procedure in patients with heart disease requiring intracardiac repair and Wolff-Parkinson-White syndrome with or without paroxysmal supraventricular tachycardia?

Although surgical division of the bundle of Kent has been reported in patients with Ebstein's anomaly[5,9] and also in patients with other structural heart disease,[5] no criteria have been defined to indicate when the procedure should be performed. On the basis of advances in cardiac mapping and surgery and our experience with the patient to be described, we discuss the indications for surgical division of free wall anomalous pathways in patients with Wolff-Parkinson-White syndrome and heart disease requiring intracardiac repair.

Case Report

A 14 year old girl was referred to our hospital because of exercise intolerance and cyanosis since age 8 months. She had never received cardiac medication and had no history of palpitations, chest pain, dizziness or syncope. Family history revealed no arrhythmia or heart disease.

Physical examination: The patient was moderately cyanotic and obese, with a regular heart rate of 88 beats/min, respiratory rate of 16/min and blood pressure of 88/60 mm Hg. There was no increased jugular venous pulsation, and the lungs were clear on auscultation. The apical impulse was displaced 3 cm to the left of the mid clavicular line at the fifth intercostal space. The first heart sound was single and the second widely split and fixed. A grade 2/6 systolic ejection murmur was heard at the mid and upper left sternal border. The peripheral pulses were of small volume, and moderate clubbing and cyanosis of the nailbeds were present.

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Laboratory tests: The hemoglobin was 28.0 g/100 ml and the hematocrit 62.8 percent. The electrocardiogram (Fig. 1A) revealed a short P-R interval (0.10 second) and delta waves characteristic of Wolff-Parkinson-White syndrome. The negative delta waves and ventricular complexes in the anterior chest leads were typical of the type B syndrome. The vectorcardiogram (Fig. 2) was consistent with this finding, revealing slow initial ventricular depolarization directed to the left.[10] The chest roentgenogram disclosed moderate cardiomegaly with decreased pulmonary vascular markings.

Cardiac catheterization results: Ebstein's anomaly was diagnosed at cardiac catheterization (Table I), and an atrial septal defect with right to left shunting (pulmonary to systemic flow ratio 0.4/1) was found. During catheterization, the atrial communication was temporarily occluded using a balloon-tipped catheter. Under these conditions, the femoral arterial saturation was 95 percent with the patient breathing room air, and the cardiac index measured with indocyanine green dye curves was 2.8 liters/min per m^2. Several episodes of paroxysmal supraventricular tachycardia occurring during the catheterization resolved spontaneously or after inducement of atrial depolarizations with the catheter. Electrophysiologic studies revealed a short His bundle to ventricle interval of 10 msec and a normal right atrium to His bundle interval of 70 msec. Neither pacing studies nor premature atrial stimulation was carried out.

First operation: Because of the progressive nature of our patient's symptoms, surgical closure of the atrial septal defect was recommended. The defect was patched, and a tricuspid valve commissurotomy was performed because the orifice appeared stenotic at operation. Before and after cardiopulmonary bypass, there were episodes of paroxysmal supraventricular tachycardia that were only intermittently responsive to (open) direct current cardioversion, but finally intravenous administration of propranolol (0.5 mg) converted the rhythm to sinus.

TABLE I

Initial Cardiac Catheterization Data

Site	Oxygen Saturation (%)	Pressure (mm Hg)
Superior vena cava	65	. . .
Right atrium	69	a = 12; v = 9 (9)
Atrialized right ventricle	66	*a = 14; v = 9
Right ventricle	67	24/4,8
Main pulmonary artery	67	20/10 (13)
Right upper pulmonary vein	97	. . .
Left atrium	74	a = 13; v = 12 (8.5)
Left ventricle	79	140/0,16
Femoral artery	79	150/90 (95)

* Simultaneous ventricular intracardiac electrocardiogram.
Values in parentheses are mean pressures.

Postoperatively, low cardiac output was initially treated with digitalis and volume replacement. Although a high central venous pressure (15 to 24 cm H_2O) was maintained, persistent hypotension with low urinary output and poor peripheral perfusion necessitated use of a continuous dopamine infusion (5 μg/kg per min) for the first 18 hours. Numerous episodes of paroxysmal supraventricular tachycardia (Fig. 1B) occurred before and during dopamine infusion.

Atrial pacing (using epicardial atrial wires placed at operation) and digitalization failed to consistently suppress the tachycardia, but administration of procainamide (300 mg intravenously for 10 minutes) was successful. Quinidine (300 mg orally every 6 hours) was substituted, and no further episodes of paroxysmal supraventricular tachycardia occurred.

Ten days postoperatively, the patient was successfully resuscitated from an unexpected cardiorespiratory arrest. Acute cardiac tamponade was suspected and confirmed by immediate aspiration of serous fluid. Reoperation was performed; a mediastinal tube was placed but 6 days later was not functioning. Reaccumulated pericardial fluid, noted in an echocardiogram, was removed at a third operation, during which two pericardial windows were created. However, low

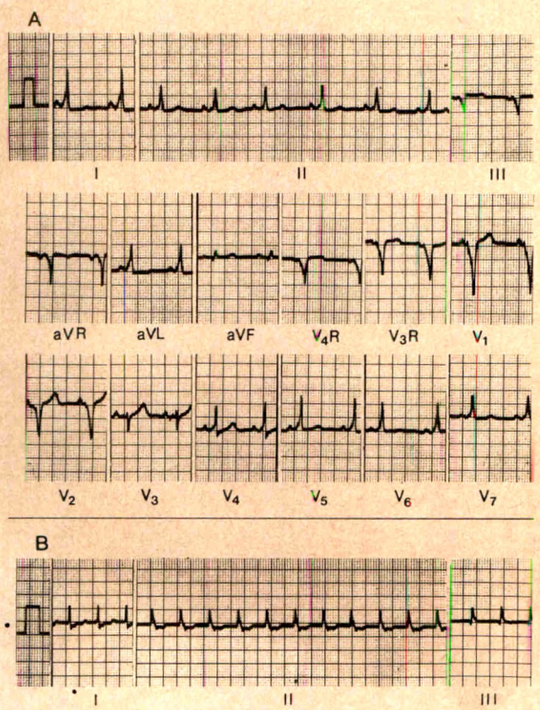

FIGURE 1. Electrocardiograms. **A,** preoperative 15 lead tracing revealing Wolff-Parkinson-White syndrome, type B. **B,** postoperative rhythm strip (leads I, II and III) showing loss of delta waves in one of the episodes of paroxysmal supraventricular tachycardia.

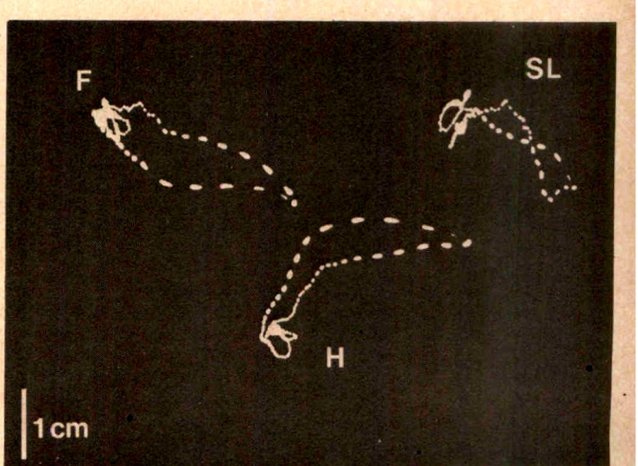

FIGURE 2. Vectorcardiogram in the frontal (F), left sagittal (SL) and horizontal (H) planes demonstrating ventricular depolarization delayed and directed to the left.

cardiac output exaggerated by numerous daily episodes of paroxysmal supraventricular tachycardia recurred, and profuse chest drainage (200 to 600 cc/day) continued. Laboratory investigations of the fluid disclosed no infectious or chylous origin.

Right atrial endocardial mapping: Four weeks after the initial operation, a repeat cardiac catheterization revealed severe tricuspid insufficiency, decreased cardiac output and an intact atrial septum. Because of severe recurrent paroxysmal supraventricular tachycardia, an attempt was made to localize the anomalous pathway. The endocardium of the right atrium was mapped during right ventricular pacing. The anterior low right atrium, near the base of the right atrial appendage, was found to be activated before any other part of the right atrium, rather than the low septal right atrium as in normal retrograde atrioventricular nodal conduction.[7]

Surgical division of the bundle of Kent: Because of severe tricuspid insufficiency, valve replacement was recommended. In light of the opportunity and the patient's severe postoperative tachycardia, elective surgical division of the bundle of Kent was also recommended. Intraoperative mapping was performed, confirming the location of the anomalous pathway predicted by intracardiac electrophysiologic studies during catheterization. The right ventricular epicardium was mapped during right atrial pacing (Fig. 3) and the right atrial epicardium during right ventricular pacing (Fig. 4) and paroxysmal supraventricular tachycardia. The points of earliest activation coincided and were located at the base of atrial appendage. The patient was placed on cardiopulmonary bypass and after insertion of a 27 mm Cooley-Cutter tricuspid prosthesis, the bundle of Kent was divided (Fig. 4). The atrialized right ventricle was not plicated.

Postoperatively, the patient has had no further episodes of paroxysmal supraventricular tachycardia, and the surface electrocardiogram has shown no evidence of Wolff-Parkinson-White syndrome (Fig. 5). There is no cyanosis and there are no signs or symptoms of congestive heart failure. The patient is active and attending school 1 year postoperatively; her only medications are Lanoxin®, 0.125 mg twice daily, and Coumadin®, 2 mg daily.

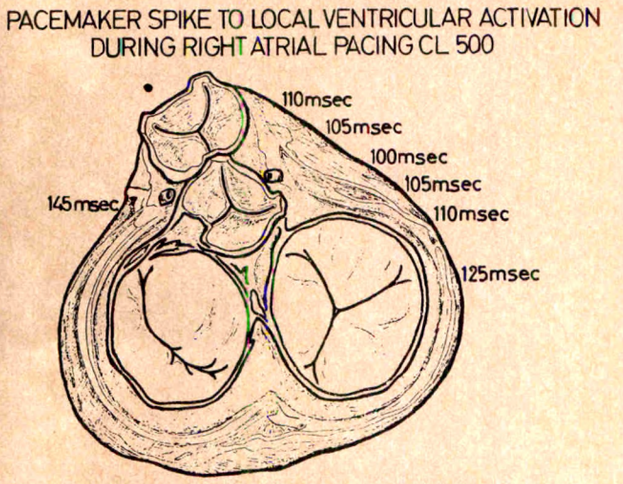

FIGURE 3. Drawing of a cross section of the heart, viewed in a superior-inferior direction, showing ventricular epicardial mapping. The numbers represent the time of local ventricular activation during right atrial pacing at a cycle length (CL) of 500 msec. The early asynchronous activation of the anterior right ventricle (100 msec) at the base of the right atrial appendage localized the bundle of Kent at that site.

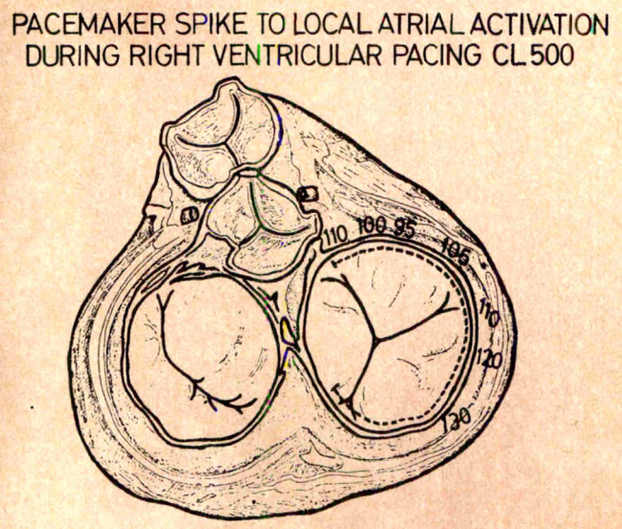

FIGURE 4. Drawing (orientation as in Fig. 3) depicting atrial epicardial mapping; the numbers represent the time (in msec) of local atrial activation during right ventricular pacing at a cycle length (CL) of 500 msec. The early activation of the right atrium at the base of the right atrial appendage coincided with that obtained from atrial epicardial mapping during supraventricular tachycardia and ventricular epicardial mapping. The **dashed line** shows the site of the endocardial to epicardial incision.

Discussion

The presence of Wolff-Parkinson-White syndrome in our patient was demonstrated in the surface electrocardiogram and confirmed at cardiac catheterization with intracardiac electrophysiologic studies. Because

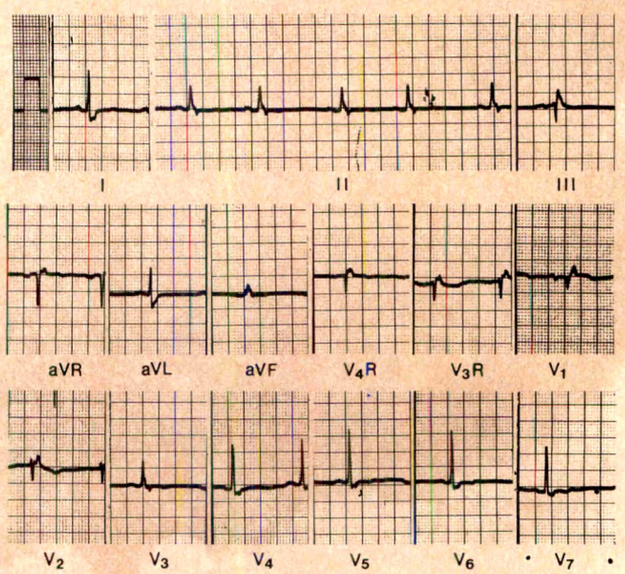

FIGURE 5. Postoperative (after tricuspid valve replacement and division of the bundle of Kent) 15 lead electrocardiogram revealing normal sinus rhythm, incomplete right bundle branch block and absence of delta waves.

the patient had no history of paroxysmal supraventricular tachycardia, surgical division of the anomalous pathway was not recommended at the time the atrial septal defect was closed. However, the many postoperative episodes of severe tachycardia indicated that surgical division of the bundle of Kent should have been performed during the initial operation. Although the supraventricular tachycardia was alleviated with procainamide and quinidine, the other postoperative complications (chronic pericardial effusion and severe right heart failure secondary to severe tricuspid insufficiency) required prosthetic replacement of the tricuspid valve.

Indications for division of anomalous pathway: Elective surgical division of the anomalous free wall pathway was considered appropriate at reoperation for several reasons: First, the debilitating episodes of supraventricular tachycardia were difficult to manage medically in the immediate postoperative periods. Second, the intracardiac reoperation required for severe tricuspid insufficiency provided an opportunity to perform the additional procedure. Finally, although our patient had not yet experienced atrial flutter or fibrillation, these arrhythmias are common postoperatively and in the presence of a Kent bundle may be transmitted to the ventricles, producing corresponding ventricular arrhythmias.[5]

Previous reports suggest that intracardiac repair alone in Ebstein's anomaly may not decrease the incidence of arrhythmia or sudden death.[2,9] The life-threatening nature of paroxysmal supraventricular tachycardia is illustrated by the patient of Rosenberg et al.[6] who had Ebstein's anomaly and Wolff-Parkinson-White syndrome and died postoperatively from tachycardia. Therefore intracardiac operation combined with surgical division of the bundle of Kent should decrease the occurrence of sudden death.

According to Gallagher et al.,[5] surgical division of free wall accessory pathways is safe and effective and the treatment of choice for refractory supraventricular tachycardia. Intracardiac electrophysiologic studies have led to the increased detection of these anomalous conduction pathways,[11] and their precise location can now be determined with intraoperative mapping.[5,7] Thus, in patients with Wolff-Parkinson-White syndrome and heart disease who have refractory supraventricular tachycardia, there is little question that the ideal treatment is surgical division of the bundle of Kent.

Indication for division of anomalous pathway in absence of history of tachycardia: The question of elective surgical division of the bundle of Kent has not previously been considered in relation to patients with Wolff-Parkinson-White syndrome who require intracardiac operation for other heart disease but have no history of tachycardia. McFaul et al.,[9] describing their surgical experience with Ebstein's anomaly, included two patients with Wolff-Parkinson-White syndrome who had successful mapping and division of the bundle of Kent at the time of intracardiac repair. Gallagher et al.,[5] reporting on surgical correction of Wolff-Parkinson-White syndrome, included six patients with Ebstein's anomaly and one with a secundum atrial septal defect but did not mention whether concomitant intracardiac repair was performed. Neither report stated whether the procedure should be recommended for all patients with Wolff-Parkinson-White syndrome requiring open heart surgery.

Implications: Although Ebstein's anomaly is one of the congenital heart defects most often associated with Wolff-Parkinson-White syndrome, other forms of heart disease coexist with this conduction abnormality.[5,12] Moreover, Ebstein's and other forms of heart disease have become increasingly amenable to intracardiac correction. On the basis of advances in mapping and surgery and our experience with this patient, we conclude that when the Wolff-Parkinson-White syndrome (even if not initially associated with paroxysmal supraventricular tachycardia) coexists with surgically treatable heart disease, elective division of the free wall anomalous pathway should be considered at the time of initial intracardiac operation. To enhance location of the anomalous pathway, this procedure should be performed in facilities equipped for endocardial mapping at cardiac catheterization and epicardial mapping at operation.

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Adult Cardiovascular Training Programs In the United States

This listing is provided as a service to physicians by the American College of Cardiology

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Cardiology Positions 1977–1978 Available	Bed Size
ALABAMA				
Birmingham 35294	University of Alabama Hospitals and Clinics	14	14	663
Birmingham 35294	Veterans Administration Hospital	. . .	. . .	497
ARIZONA				
Phoenix 85062	Good Samaritan Hospital	6	6	695
Phoenix 85008	Maricopa County General Hospital	3	3	500
Phoenix 85013	St. Joseph's Hospital and Medical Center		No Response	
Tucson 85724	University of Arizona Health Science Center	6	6	300
Tucson 85723	Veterans Administration Hospital	. . .	. . .	450
Tucson 85723	Southern Memorial Hospital (Las Vegas, Nevada)	. . .	. . .	300
ARKANSAS				
Little Rock 72206	University of Arkansas Medical Center	7	7	391
Little Rock 72206	Veterans Administration Hospital	. . .	. . .	460
CALIFORNIA				
Davis 95616	University of California at Davis Hospital	12	12	500
Fairfield 94535	David Grant U. S. Air Force Medical Center		No Response	
Fresno 93702	Valley Medical Center of Fresno		No Response	
Loma Linda 92354	Loma Linda University Hospital	2	2	525
Long Beach 90801	Memorial Hospital Medical Center	6	6	850
Long Beach 90813	St. Mary's Long Beach Hospital		No Response	
Los Angeles 90048	Cedars-Sinai Medical Center	12	12	1140
Los Angeles 90029	Cedars of Lebanon Hospital Division	. . .	. . .	. . .
Los Angeles 90048	Mt. Sinai Hospital Division	. . .	. . .	. . .
Los Angeles 90017	Hospital of the Good Samaritan Medical Center		No Response	
Los Angeles 90027	Kaiser Foundation Hospital		No Response	
Los Angeles 90059	Martin Luther King, Jr. General Hospital		No Response	
Los Angeles 90024	UCLA Medical Center	8	8	800
Los Angeles 90033	University of Southern California and the Los Angeles County–USC Medical Center	10	10	3976
Los Angeles 90073	Veterans Administration–Wadsworth Hospital Center	6	6	850
Los Angeles 90033	White Memorial Medical Center	2	2	367
Martinez 94553	Veterans Administration Hospital	3	3	450
Orange 92668	University of California–Irving Medical Center	8	8	481
Long Beach 90801	Veterans Administration Hospital	. . .	. . .	1100
Pasadena 91105	Huntington Memorial Hospital	2	2	563
Sacramento 95817	Sacramento Medical Center		No Response	
San Diego 92103	Mercy Hospital and Medical Center	1	2	512
San Diego 92134	Naval Regional Medical Center	3	4	1000
San Diego 92103	University Hospital of San Diego County	7	7	350
San Diego 92103	Veterans Administration Hospital	. . .	. . .	450
San Francisco 94129	Letterman Army Medical Center	4	4	500
San Francisco 94120	Mount Zion Hospital & Medical Center	1	2	449
San Francisco 94120	Presbyterian Hospital of Pacific Medical Center	7	7	340
San Francisco 94110	San Francisco General Hospital	2	2	650
San Francisco 94143	University of California, San Francisco-Moffitt Hospital	7	8	550
San Francisco 94118	U. S. Public Health Service Hospital		No Response	
San Francisco 94121	Veterans Administration Hospital		No Response	
San Jose 95128	Santa Clara Valley Medical Center		No Response	
Sepulveda 91343	UCLA-San Fernando Valley Medical Program	3	3	. . .
Sepulveda 91343	Olive View Medical Center	. . .	. . .	80
Sepulveda 91343	Veterans Administration Hospital	. . .	. . .	848
Stanford 94305	Stanford University Hospital	20	20	625
Stanford 94305	Veterans Administration Hospital	. . .	. . .	2000
Torrance 90509	Harbor General Hospital	6	6	700
COLORADO				
Denver 80204	Denver General Hospital		No Response	
Denver 80240	Fitzsimons Army Medical Center		No Response	
Denver 80220	University of Colorado Medical Center		No Response	
Denver 80220	Veterans Administration Hospital		No Response	

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.

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State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Cardiology Positions 1977–1978 Available	Bed Size
CONNECTICUT				
Bridgeport 06602	Bridgeport Hospital	2	2	650
Bridgeport 06606	St. Vincents Medical Center		No Response	
Farmington 06032	Dempsey Hospital–University of Connecticut Health Center	1	1	220
Hartford 06115	Hartford Hospital	3	3	925
Hartford 06112	Mount Sinai Hospital	1	1	375
Hartford 06105	St. Francis Hospital	3	3	650
New Haven 06511	Hospital of St. Raphael	2	2	500
New Haven 06510	Yale University Medical Center	10	10	882
West Haven 06516	Veterans Administration Hospital	4	4	696
Norwalk 06856	Norwalk Hospital	2	2	450
Waterbury 06720	Waterbury Hospital	1	1	500
Waterbury 06720	St. Mary's Hospital		No Response	
DELAWARE				
Wilmington 19899	Wilmington Medical Center		No Response	
DISTRICT OF COLUMBIA				
Washington, D.C. 20003	D.C. General Hospital	2	2	645
Washington, D.C. 20001	Freedmens Hospital		No Response	
Washington, D.C. 20037	George Washington University Hospital	9	9	550
Washington, D.C. 20007	Georgetown University Hospital	8	8	500
Washington, D.C. 20060	Howard University Hospital	3	5	500
Washington, D.C. 20017	Providence Hospital	1	1	375
Washington, D.C. 20422	Veterans Administration Hospital	3	3	708
Washington, D.C. 20012	Walter Reed Army Medical Center		No Response	
Washington, D.C. 20012	Washington Hospital Center		No Response	
FLORIDA				
Gainesville 32610	University of Florida Hospital	9	9	800
Gainesville 32601	Veterans Administration Hospital		No Response	
Jacksonville 32209	University Hospital, Jacksonville	2	2	364
Miami 33152	University of Miami School of Medicine	13	13	. . .
Miami 33152	Jackson Memorial Hospital	. . .	. . .	1250
Miami 33152	Veterans Administration Hospital	. . .	. . .	1000
Miami 33152	University of Miami Hospital	. . .	. . .	80
Miami Beach 33140	Mt. Sinai Medical Center	9	9	650
Pensacola 32501	University Hospital, Pensacola		No Response	
Tampa 33612	University of South Florida Affilliated Hospitals	4	4	. . .
Tampa 33606	Tampa General Hospital	. . .	. . .	586
Tampa 33612	Veterans Administration Hospital	. . .	. . .	697
GEORGIA				
Atlanta 30303	Emory University Hospitals		No Response	
Atlanta 30303	Grady Memorial Hospital		No Response	
Atlanta 30303	Crawford W. Long Hospital		No Response	
Decatur 30033	Veterans Administration Hospital		No Response	
Atlanta 30312	Georgia Baptist Hospital	1	1	600
Augusta 30901	Medical College of Georgia Hospitals	6	6	800
Augusta 30902	Talmadge Memorial Hospital		No Response	
Augusta 30904	Veterans Administration Hospital		No Response	
Savannah 31405	Memorial Medical Center		No Response	
HAWAII				
Honolulu 96813	Queen's Medical Center		No Response	
ILLINOIS				
Chicago 60680	Abraham Lincoln School of Medicine	12	12	500
Chicago 60612	Chicago Medical School of Medicine	2	2	450
North Chicago 60064	Veterans Administration Hospital	. . .	. . .	. . .
Chicago 60614	Columbus Hospital	2	2	700
Chicago 60612	Cook County Hosiptal	7	7	1483
Chicago 60616	Mercy Hospital and Medical Center	3	3	530
Chicago 60616	Michael Reese Hospital and Medical Center	8	8	985
Chicago 60608	Mount Sinai Hospital Medical Center	4	4	460
Chicago 60611	Northwestern University Hospitals	7	7	1800
Chicago 60612	Rush-Presbyterian St. Luke's Medical Center	6	6	864
Chicago 60637	University of Chicago Hospitals	19	19	700
Chicago 60612	University of Illinois Hospital		No Response	
Chicago 60612	West Side Veterans Administration Hospital		No Response	
Evanston 60202	St. Francis Hospital		No Response	
Hines 60141	Veterans Administration Hospital		No Response	
Maywood 60153	Loyola University Hospital		No Response	
INDIANA				
Indianapolis 46202	Indiana University Hospitals	18	18	1500
Indianapolis 46202	Methodist Hospital Graduate Medical Center	3	3	1150
Indianapolis 46260	St. Vincent Hospital	2	2	580
IOWA				
Iowa City 52242	University of Iowa Hospitals and Clinics	11	11	1000
Iowa City 52240	Veterans Administration Hospital	. . .	. . .	500
KANSAS				
Kansas City 66103	University of Kansas Medical Center	2	4	600

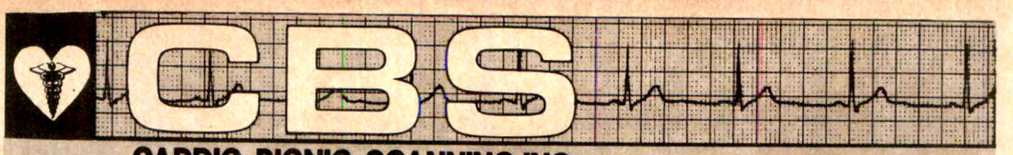
State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Cardiology Positions 1977–1978 Available	Bed Size
KENTUCKY				
Lexington 40506	University of Kentucky Medical Center	11	11	430
Louisville 40217	St. Joseph's Infirmary		No Response	
Louisville 40202	University of Louisville Affiliated Hospitals	10	10	...
Louisville 40202	Jewish Hospital	...	...	441
Louisville 40202	Louisville General Hospital	...	...	370
Louisville 40202	Norton Hospital	...	...	492
Louisville 40202	Veterans Administration Hospital	...	...	444
LOUISIANA				
New Orleans 70112	Hotel Dieu Hospital		No Response	
New Orleans 70112	Louisiana State University Medical Center	4	4	1400
New Orleans 70121	Ochsner Clinic	3	6	420
New Orleans 70112	Tulane University Medical Center	14	14	...
New Orleans 70112	Charity Hospital	...	...	1000
New Orleans 70112	University Hospital	...	...	300
New Orleans 70112	Touro Infirmary	...	...	570
New Orleans 70112	Veterans Administration Hospital	...	...	...
Shreveport 71130	Louisiana State University, Shreveport		No Response	
MAINE				
Portland 04102	Maine Medical Center	3	3	565
MARYLAND				
Baltimore 21224	Baltimore City Hospital		No Response	
Baltimore 21205	Johns Hopkins Hospital	21	21	1050
Baltimore 21201	Maryland General Hospital	1	2	485
Baltimore 21202	Mercy Hospital		No Response	
Baltimore 21215	Sinai Hospital of Baltimore	0	0	500
Baltimore 21211	U.S. Public Health Service Hospital	2	2	200
Baltimore 21201	University of Maryland Hospital	5	5	800
Bethesda 20014	National Naval Medical Center	4	4	550
Cheverly 20785	Prince George's General Hospital	2	2	600
MASSACHUSETTS				
Boston 02215	Beth Israel Hospital–Harvard Medical School	5	5	432
Boston 02118	Boston University Medical Center	13	13	800
Boston 02118	Boston City Hospital	...	...	...
Boston 02118	University Hospital	...	...	...
Boston 02130	Boston Veterans Administration Hospital	3	3	800
Boston 02124	Carney Hospital	1	1	376
Boston 02114	Massachusetts General Hospital	12	12	1100
Boston 02215	New England Deaconess Hospital	0	6	450
Boston 02115	Peter Bent Brigham Hospital	16	16	350
Boston 02135	St. Elizabeth Hospital	5	5	385
Boston 02111	Tufts/New England Medical Center Hospital		No Response	
Cambridge 02138	Mount Auburn Hospital	2	2	300
Pittsfield 01201	Berkshire Medical Center	1	1	415
Springfield 01106	Bay State Medical Center	1	2	1036
Springfield 01107	Springfield Hospital Medical Center		No Response	
West Roxbury 02132	West Roxbury Veterans Hospital	6	6	280
Worcester 01605	University of Massachusetts Affiliated Hospitals	11	11	...
Worcester 01605	University of Massachusetts Hospital	...	...	175
Worcester 01605	Memorial Hospital	...	...	400
Worcester 01604	St. Vincent Hospital	...	...	600
Worcester 01610	Worcester City Hospital	...	...	350
MICHIGAN				
Allen Park 48101	Veterans Administration Hospital		No Response	
Ann Arbor 48109	University of Michigan Medical Center	15	15	...
Ann Arbor 48104	St. Joseph Mercy Hospital	...	...	558
Ann Arbor 48109	University Hospital	...	...	960
Ann Arbor 48105	Veterans Administration Hospital	...	...	430
Ann Arbor 48132	Wayne County General Hospital	...	...	441
Detroit 48226	Detroit General Hospital		No Response	
Detroit 48202	Henry Ford Hospital	9	9	1100
Detroit 48235	Mount Carmel Mercy Hospital	1	1	570
Detroit 48236	St. John Hospital	4	4	528
Detroit 48235	Sinai Hospital	5	5	619
Detroit 48201	Wayne State University Hospitals	12	12	...
Detroit 48226	Detroit General Hospital	...	...	435
Detroit 48201	Harper-Grace Hospital	...	...	999
Detroit 48201	Hutzel Hospital	...	...	387
Detroit 48201	Veterans Administration Hospital	...	...	639
Flint 48502	Hurley Hospital		No Response	
Royal Oak 48072	William Beaumont Hospital	6	6	940
Southfield 48075	Providence Hospital	2	2	403
MINNESOTA				
Minneapolis 55455	University of Minnesota Hospitals	14	14	790
Minneapolis 55415	Hennepin County Medical Center	...	...	485
St. Paul 55101	St. Paul-Ramsey Hospital	...	...	610
Minneapolis 55417	Veterans Administration Hospital	...	...	775

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Cardiology Positions 1977–1978 Available	Bed Size
MINNESOTA (cont'd)				
Rochester 55901	Mayo Clinic	13	13	...
Rochester 55901	Methodist Hospital	...	...	770
Rochester 55901	St. Mary's Hospital	...	...	983
MISSISSIPPI				
Jackson 39216	University Hospital		No Response	
Jackson 39216	Veterans Administration Hospital		No Response	
MISSOURI				
Columbia 65201	University of Missouri Medical Center	4	4	499
Columbia 65201	Harry S. Truman Memorial VA Hospital	...	...	406
Kansas City 64111	St. Luke's Hospital	3	3	665
St. Louis 63110	Jewish Hospital of St. Louis	8	8	587
St. Louis 63104	St. Louis City Hospital		No Response	
St. Louis 63104	St. Louis University Medical Schools	11	11	...
St. Louis 63141	St. John's Mercy Medical Center	...	...	607
St. Louis 63104	St. Louis University Hospital	...	...	335
St. Louis 63104	Veterans Administration Hospital	...	...	388
St. Louis 63112	St. Luke's Hospital	1	1	261
St. Louis 63110	Washington University School of Medicine, Barnes Hospital	10	10	1200
NEBRASKA				
Omaha 68108	Creighton University Medical Center	5	5	...
Omaha 68108	St. Joseph Hospital	...	...	585
Omaha 68105	Veterans Administration Hospital	...	...	446
Omaha 68105	University of Nebraska Medical Center	2	4	320
NEW HAMPSHIRE				
Hanover 03755	Darthmouth Hitchcock Medical Center, Mary Hitchcock Memorial Hospital		No Response	
NEW JERSEY				
Brown Mills 08015	Deborah Heart & Lung Center (affiliated with Albert Einstein Medical Center, Philadelphia, Pennsylvania)	20	20	132
East Orange 07019	Veterans Administration Hospital	4	4	1200
Hackensack 07601	Hackensack Hospital	2	2	500
Jersey City 07304	Jersey City Medical Center		No Response	
Livingston 07939	St. Barnabas Medical Center		No Response	
Long Branch 07740	Monmouth Medical Center		No Response	
New Brunswick 08903	New Brunswick Affiliated Hospitals	1	1	...
New Brunswick 08903	Middlesex Hospital	...	...	370
New Brunswick 08903	St. Peters's Hospital	...	...	420
Newark 07103	College of Medicine & Dentistry of New Jersey/New Jersey Medical School	5	5	650
Newark 07107	Martland Hospital		No Response	
Newark 07112	Newark Beth Israel Medical Center	5	5	500
Newark 07102	St. Michael's Medical Center	5	5	480
Paramus 07652	Bergen Pines County Hospital		No Response	
Paterson 07503	St. Joseph's Hospital & Medical Center	2	2	530
Piscataway 08854	Raritan Valley Hospital–Rutgers Medical School		No Response	
Summit 07901	Overlook Hospital	1	1	541
NEW MEXICO				
Albuquerque 87131	University of New Mexico Affiliated Hospitals	4	4	...
Albuquerque 87106	Bernalillo County Medical Center	...	...	237
Albuquerque 87108	Lovelace-Bataan Medical Center	...	...	256
Albuquerque 87106	Veterans Administration Hospital	...	...	442
NEW YORK				
Albany 12208	Albany Medical College	2	2	900
Albany 12208	Veterans Administration Hospital	2	2	750
Bronx 10461	Albert Einstein College of Medicine	8	8	400
Bronx 10461	Bronx Municipal Hospital Center	...	...	900
Bronx 10456	Bronx-Lebanon Hospital Center	3	3	568
Bronx 10466	Miscericordia Hospital Medical Center–Lincoln Hospital Affiliation		No Response	
Bronx 10467	Montefiore Hospital and Medical Center	10	10	800
Bronx 10467	North Central Bronx	...	...	360
Brooklyn 11212	Brookdale Hospital Medical Center	5	5	1031
Brooklyn 11201	Brooklyn Hospital	4	4	500
Brooklyn 11201	Brooklyn Cumberland Medical Center	...	...	500
Brooklyn 11235	Coney Island Hospital	4	4	560
Brooklyn 11203	Kings County Medical Center	5	5	1300
Brooklyn 11203	Downstate Medical Center	...	...	350
Brooklyn 11211	Greenpoint Hospital		No Response	
Brooklyn 11203	Kingsbrook Jewish Medical Center	2	2	800
Brooklyn 11219	Maimonides Medical Center	4	4	614
Brooklyn 11215	Methodist Hospital	2	2	557
Brooklyn 11209	Veterans Administration Hospital	3	3	1000
Buffalo 14203	Buffalo General Hospital		No Response	
Buffalo 14209	Millard Fillmore Hospital	1	2	711
Buffalo 14215	State University of New York at Buffalo, Edward J. Meyer Memorial Hospital	2	2	700

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Cardiology Positions 1977–1978 Available	Bed Size
NEW YORK (cont'd)				
Buffalo 14215	Veterans Administration Hospital	4	4	800
East Meadow 11554	Nassau County Medical Center	3	3	650
Jamaica 11432	Catholic Medical Center	2	2	. . .
Jamaica 11432	Mary Immaculate Hospital	. . .	. . .	280
Jamaica 11432	Queens General Hospital	. . .	. . .	800
Jamaica 11418	Jamaica Hospital	1	1	250
Jamaica 11432	State University of New York at Stony Brook		No Response	
Manhasset 11030	North Shore University Hospital	4	4	600
Mineola 11501	Nassau Hospital		No Response	
New Hyde Park 11040	Long Island Jewish–Hillside Medical Center	4	4	650
New York 10003	Beth Israel Medical Center	4	4	1028
New York 10003	Cabrini Health Care Center	1	1	478
New York 11373	City Hospital Center at Elmhurst		No Response	
New York 10458	Fordham Hospital		No Response	
New York 10037	Harlem Hospital		No Response	
New York 10021	Lenox Hill Hospital	5	5	680
New York 11201	Long Island College Hospital		No Response	
New York 10021	Memorial Sloan–Kettering Cancer Center		No Response	
New York 10452	Morrisania City Hospital		No Response	
New York 10029	Mt. Sinai Hospital & Medical School	12	12	1300
New York 10021	New York Hospital–Cornell Medical Center	5	5	1000
New York 10029	New York Medical College		No Response	
New York 10029	Flower and Fifth Avenue Hospital		No Response	
New York 10029	Metropolitan Hospital		No Response	
New York 10016	New York University School of Medicine	6	6	. . .
New York 10016	Bellevue Hospital	. . .	. . .	1319
New York 10016	New York University Hospital	. . .	. . .	781
New York 10032	Presbyterian Hospital		No Response	
New York 11432	Queens Hospital Center		No Response	
New York 10019	Roosevelt Hospital	2	2	600
New York 10025	St. Luke's Hospital Center	6	6	788
New York 10011	St. Vincent's Hospital & Medical Center	4	4	813
New York 11213	State University Hospital		No Response	
New York 10468	Veterans Administration Hospital (Bronx)		No Response	
New York 10010	Veterans Administration Hospital (Manhattan)	4	4	1000
Northport 11768	Northport Veterans Administration Hospital	2	2	850
Rochester 14607	Genesee Hospital		No Response	
Rochester 14620	Highland Hospital		No Response	
Rochester 14611	St. Mary's Hospital	1	1	300
Rochester 14642	University of Rochester School of Medicine	9	9	700
Rochester 14641	Strong Memorial Hospital	. . .	. . .	. . .
Rochester 14621	Rochester General Hospital	1	2	450
Staten Island 10304	U.S. Public Health Service Hospital	4	4	500
Syracuse 13210	Upstate Medical Center-State University of New York	6	6	. . .
Syracuse 13210	University Hospital	. . .	. . .	350
Syracuse 13210	Veterans Administration Hospital	. . .	. . .	600
NORTH CAROLINA				
Chapel Hill 27514	University of North Carolina School of Medicine	8	8	600
Chapel Hill 27514	North Carolina Memorial Hospital		No Response	
Charlotte 28203	Charlotte Memorial Hospital		No Response	
Durham 27710	Duke University Medical Center	28	28	. . .
Durham 27706	Duke University Hospital	. . .	. . .	895
Durham 27706	Veterans Administration Hospital	. . .	. . .	500
Winston-Salem 27103	Bowman Gray School of Medicine	5	5	675
Winston-Salem 27103	Bowman Gray Medical Center	. . .	. . .	. . .
Winston-Salem 27103	North Carolina Baptist Hospital	. . .	. . .	. . .
OHIO				
Akron 44309	Akron City Hospital	1	1	650
Akron 44307	Akron General Medical Center		No Response	
Cincinnati 45220	Good Samaritan Hospital	1	1	750
Cincinnati 45229	Jewish Hospital	1	1	625
Cincinnati 45267	University of Cincinnati Medical Center	7	7	. . .
Cincinnati 45267	Cincinnati General Hospital	. . .	. . .	690
Cincinnati 45267	Veterans Administration Hospital	. . .	. . .	413
Cleveland 44106	Cleveland Clinic Educational Foundation	39	39	1010
Cleveland 44109	Cleveland Metropolitan General Hospital	4	4	580
Cleveland 44112	Huron Road Hospital		No Response	
Cleveland 44113	Lutheran Medical Center	2	2	390
Cleveland 44106	Mount Sinai Hospital	3	3	550
Cleveland 44104	St. Luke's Hospital	1	1	550
Cleveland 44106	University Hospitals of Cleveland	8	8	. . .
Cleveland 44106	University Hospital	. . .	. . .	1000
Cleveland 44106	Veterans Administration Hospital	. . .	. . .	700
Columbus 43222	Mt. Carmel Medical Center	2	2	510
Columbus 43210	Ohio State University–College of Medicine	9	9	1040
Columbus 43214	Riverside Methodist Hospital	2	2	850

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Cardiology Positions 1977–1978 Available	Bed Size
OHIO (cont'd)				
Dayton 45406	Good Samaritan Hospital	0	2	550
Dayton 45409	Miami Valley Hospital		No Response	
Kettering 45429	Kettering Medical Center	0	2	472
Toledo 43606	Toledo Hospital	2	3	775
Youngstown 44501	St. Elizabeth Hospital Medical Center	1	2	750
Youngstown 44502	Youngstown Hospital	2	2	950
OKLAHOMA				
Oklahoma City 73190	University of Oklahoma Health Sciences Center	4	6	...
Oklahoma City 73190	University Hospitals & Clinics	...	...	344
Oklahoma City 73104	Veterans Administration Hospital	...	...	463
OREGON				
Portland 97201	University of Oregon Health Sciences Center	9	9	...
Portland 97201	University Hospital	...	...	450
Portland 97207	Veterans Administration Hospital	...	...	550
PENNSYLVANIA				
Allentown 18104	Allentown and Sacred Heart Hospital Center	1	1	350
Allentown 18104	Allentown Hospital	...	...	280
Danville 17821	Geisinger Medical Center	3	3	500
Harrisburg 17101	Harrisburg Hospital	1	1	490
Hershey 17033	Milton S. Hershey Medical Center	7	7	350
Johnstown 15905	Conemaugh Valley Memorial Hospital		No Response	
Philadelphia 19141	Albert Einstein Medical Center	20	20	619
Browns Mill, New Jersey 08015	Deborah Heart & Lung Center	...	...	132
Philadelphia 19125	Episcopal Hospital	1	1	357
Philadelphia 19146	Graduate Hospital	2	2	300
Philadelphia 19102	Hahnemann Medical College & Hospital	9	9	450
Chester 19013	Crozer-Chester Hospital	...	...	400
Philadelphia 19145	St. Agnes Hospital	...	...	350
Philadelphia 19107	Jefferson Medical Center	7	7	500
Philadelphia 19151	Lankenau Hospital	6	6	450
Philadelphia 19129	Medical College of Pennsylvania Hospital	8	8	345
Philadelphia 19143	Mercy Catholic Medical Center		No Response	
Philadelphia 19145	Naval Hospital		No Response	
Philadelphia 19107	Pennsylvania Hospital	1	1	425
Philadelphia 19104	Philadelphia General Hospital		No Response	
Philadelphia 19104	Presbyterian-University of Pennsylvania Medical Center	5	5	425
Philadelphia 19140	Temple University	12	12	533
Philadelphia 19107	Thomas Jefferson University Hospital		No Response	
Philadelphia 19104	Hospital of the University of Pennsylvania	11	11	694
Philadelphia 19104	Veterans Administration Hospital	...	...	348
Pittsburgh 15212	Allegheny General Hospital	6	7	700
Pittsburgh 15219	Mercy Hospital		No Response	
Pittsburgh 15213	University of Pittsburgh School of Medicine	3	3	...
Pittsburgh 15213	Montefiore Hospital	...	...	433
Pittsburgh 15201	St. Francis General Hospital	3	3	900
Pittsburgh 15232	Shadyside Hospital	1	2	450
Pittsburgh 15261	University of Pittsburgh Health Center Hospitals	7	7	...
Pittsburgh 15261	Presbyterian-University Hospital	...	...	220
Pittsburgh 15261	Veterans Administration Hospital (Oakland Division)	...	...	160
Pittsburgh 15224	Western Pennsylvania Hospital	0	2	680
Sayre 18840	Guthrie Clinic/Robert Packer Hospital	1	1	306
PUERTO RICO				
Mayaguez 00708	Mayaguez Medical Center		No Response	
Ponce 00731	Ponce District General Hospital	4	4	541
San Juan 00936	University District Hospital		No Response	
San Juan 00936	Veterans Administration Hospital	2	2	750
RHODE ISLAND				
Providence 02906	Miriam Hospital	3	3	247
Providence 02902	Rhode Island Hospital	5	5	720
Providence 02908	Veterans Administration Hospital	0	0	353
SOUTH CAROLINA				
Charleston 29403	Medical University of South Carolina	6	6	...
Charleston 29403	Charleston County Hospital	...	...	151
Charleston 29403	Medical University Hospital	...	...	493
Charleston 29403	Veterans Administration Hospital	...	...	388
TENNESSEE				
Chattanooga 37403	University of Tennessee College of Medicine	1	1	750
Chattanooga 37402	T. E. Thompson & Baroness Erlanger Hospital	...	...	...
Memphis 38163	University of Tennessee Health Science Center	5	5	...
Memphis 38163	Baptist Memorial	...	...	1601
Memphis 38163	City of Memphis Hospital	...	...	659
Memphis 38163	University of Tennessee Hospital	...	...	230
Memphis 38163	Veterans Administration Hospital	...	...	983
Nashville 37208	Meharry Medical College		No Response	

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1977–1978 Filled	Available	Bed Size
TENNESSEE (cont'd)				
Nashville 37232	Vanderbilt University Hospitals	7	7	...
Nashville 37232	Metro General Hospital	...	...	210
Nashville 37232	St. Thomas Hospital	...	...	410
Nashville 37232	Vanderbilt University Hospital	...	...	500
Nashville 37232	Veterans Administration Hospital	...	...	500
TEXAS				
Dallas 75246	Baylor University Medical Center	6	6	1300
Dallas 75222	Methodist Hospital of Dallas	3	3	508
Dallas 75235	University of Texas Health Science Center at Dallas	17	17	...
Dallas 75235	Children's Hospital	...	...	117
Dallas 75235	Parkland Hospital	...	...	902
Dallas 75235	Presbyterian Hospital	...	...	700
Dallas 75235	St. Paul's Hospital	...	...	489
Dallas 75235	Veterans Administration Hospital	...	...	739
Ft. Sam Houston 78234	Brooke Army Medical Center	3	3	564
Galveston 77550	University of Texas Medical Branch	2	2	1100
Houston 77030	Baylor College of Medicine	16	16	...
Houston 77030	Ben Taub Hospital	...	...	475
Houston 77030	Methodist Hospital	...	...	929
Houston 77030	Veterans Administration Hospital	...	...	1296
Houston 77025	St. Luke's Episcopal Hospital	12	14	757
Houston 77030	University of Texas Medical School at Houston		No Response	
Houston 77030	Herman Hospital		No Response	
San Antonio 78284	University of Texas Health Science Center	7	7	...
San Antonio 78284	Bexar County Hospital	...	...	700
San Antonio 78284	Veterans Administration Hospital	...	...	493
San Antonio 78236	Wilford Hall USAF Medical Center Lackland Air Force Base		No Response	
Temple 76501	Scott and White Memorial Hospital	1	1	425
UTAH				
Salt Lake City 84132	University of Utah Medical Center and Affiliated Hospitals	9	9	...
Salt Lake City 84132	Holy Cross Hospital	...	...	343
Salt Lake City 84132	Latter Day Saints Hospital	...	...	570
Salt Lake City 84132	University of Utah Hospital	...	...	310
Salt Lake City 84132	Veterans Administration Hospital	...	...	506
VERMONT				
Burlington 05401	University of Vermont College of Medicine	4	4	600
VIRGINIA				
Charlottesville 22901	University of Virginia Hospital	5	5	692
Richmond 23298	Medical College of Virginia	9	9	1000
Richmond 23298	Veterans Administration Hospital	...	...	1000
WASHINGTON				
Seattle 98195	University of Washington Hospitals	9	9	...
Seattle 98104	Harborview Medical Center	...	...	300
Seattle 98195	Providence Hospital	...	...	300
Seattle 98195	University Hospital	...	...	310
Seattle 98195	USPHS Hospital	...	...	280
Seattle 98195	Veterans Administration Hospital	...	...	320
WEST VIRGINIA				
Morgantown 26506	West Virginia University Medical Center		No Response	
WISCONSIN				
Madison 53706	University of Wisconsin Hospitals	4	4	...
Madison 53705	Veterans Administration Hospital	...	...	424
Milwaukee 53226	Medical College of Wisconsin	7	7	...
Milwaukee 53226	Milwaukee County Hospital	...	...	695
Milwaukee 53226	St. Luke's Hospital	...	...	525
Milwaukee 53226	Veterans Administration Hospital	...	...	850
Milwaukee 53201	Mount Sinai Medical Center	4	4	385



CARDIO-BIONIC-SCANNING INC.

SCANNING DATA SHEET

PATIENT _____ DATE 10/10/77 - 10/11/77

ADDRESS _____ SEX _____ AGE _____

HOSPITAL Hospital I.D. # _____

PHYSICIAN _____

QUALITY OF RECORDING	PATIENT DIARY SUBMITTED	SYMPTOMS REPORTED	CALIBRATIONS
[X] GOOD [ ] FAIR [ ] POOR	[X] YES [ ] NO	[X] YES [ ] NO	[X] YES [ ] NO

HOUR	VENTRICULAR * ECTOPIC BEATS	PVC'S * PER 1000 BEATS	SUPRAVENTRICULAR ECTOPIC BEATS	ST-T CHANGES IN MM	TOTAL BEATS	RATE
4-5pm	5	3	0	-0.5		62
5-6	7	4	21	0		68
6-7	16	7	10	-1.0	total	66
7-8	12	5	1	-0.5	beats:	68
8-9	24	10	5	0	87088	62
9-10	18	8	2	0		65
10-11	30	11	3	0		61
11-12	15	7	3	**		58
12-1 am	35	13	4	**		50
1-2	61	20	0	0		57
2-3	20	9	2	-0.5		59
3-4	19	8	4	+1,0		51
4-5	11	5	2	+1.5		49
5-6	3	10	5	**		52
6-7	40	16	1	-1.0		57
7-8	19	8	1	-1.0		70
8-9	19	28	0	-0.5		77
9-10	68	29	5	-1.0		69
10-11	25	10	1	-0.5		68
11-12	18	8	1	-1.0		64
12-1 pm	7	4	0	-0.5		74
1-2	13	6	3	-0.5		66
2-3	2	2	12	-0.5		70

HEART RATE

MAXIMUM OF *159 BEATS PER MINUTE AT 12:24am MINIMUM OF **30 BEATS PER MINUTE AT 11:53am

*starts & ends abruptly, 3.8 sec. longest R-R interval @ 4:12pm, 3.04 sec.

**see writeouts.

Peter L Bond/md

THIS IS NOT A PHYSICIAN'S INTERPETATION – ONLY SUPPLEMENTAL INFORMATION TO THE DATA SCANNING STRIPS.

* (Premature Ventricular Contractions (PVC's) and Premature Supraventricular Contractions with Aberrant IV Conduction)

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ne disquieting facts: "the
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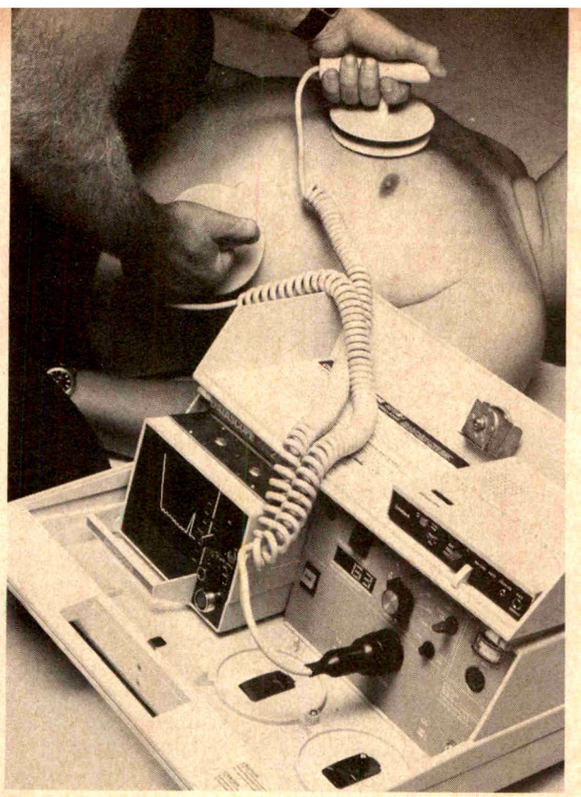
ity of defibrillating a sub-
who weighs over 220
nds is extremely low."*
se studies have produced
following finding: "virtu-
all defibrillators now in
have inadequate output
efibrillate many human
lts..."*



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It is the only defibrillator in the world that
ls the current delivered
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duces current. But
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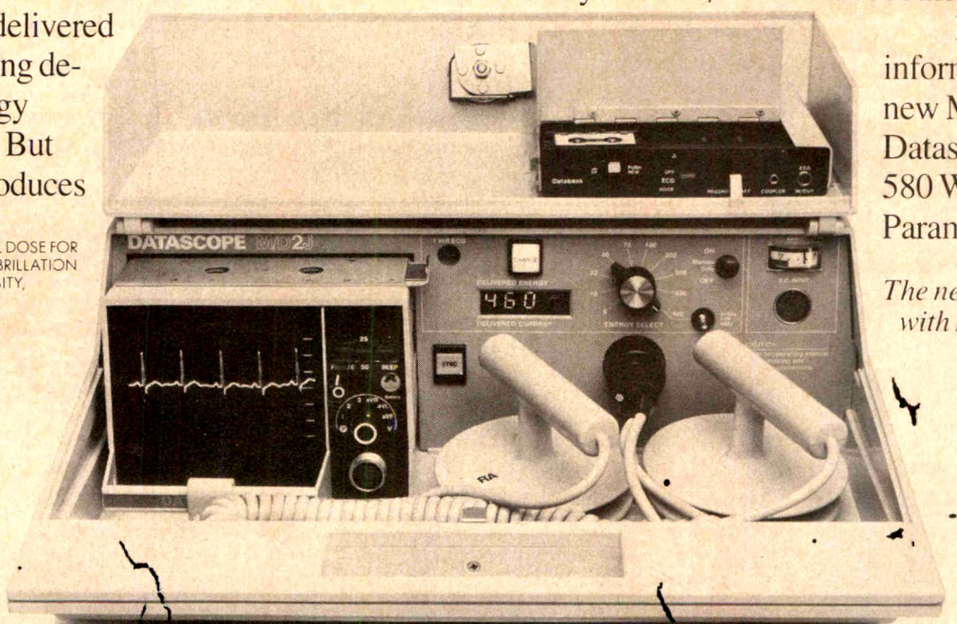

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with Databank.

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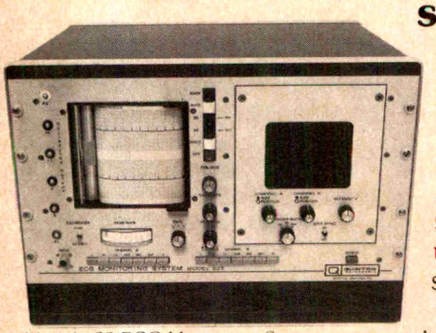

Model 623 ECG Monitoring System

The Quinton Model 623 gives you pushbutton lead selection and lets you display and record any two leads simultaneously. With the QRS Sync feature, each consecutive QRS complex can be expanded to the full width of the screen, making even small changes obvious immediately.

No battery packs are required with the 623 and the internal calibration system not only checks the recorder before you conduct a test, it also checks the oscilloscope, patient cables and heart rate meter to assure you of total system accuracy.

Build the system as your practice grows. Quinton offers a number of special purpose units which will expand the system's capabilities as your needs grow.

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A Quinton programmer allows you to concentrate on the monitor and the patient while the test progresses automatically.

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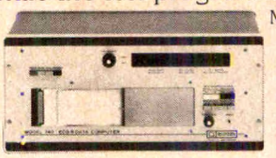
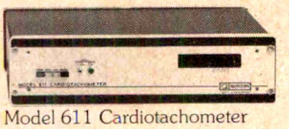


Model 740 ECG Data Computer



Model 611 Cardiotachometer

The Quinton cardiotachometer computes and digitally displays heartrate on an instantaneous, beat-by-beat basis. For details on all these products, contact Quinton Instrument Co., Dept. E16, 2121 Terry Avenue, Seattle, Washington 98121. Call 206/223-7373 or dial toll free 800-426-0538. **QUINTON**

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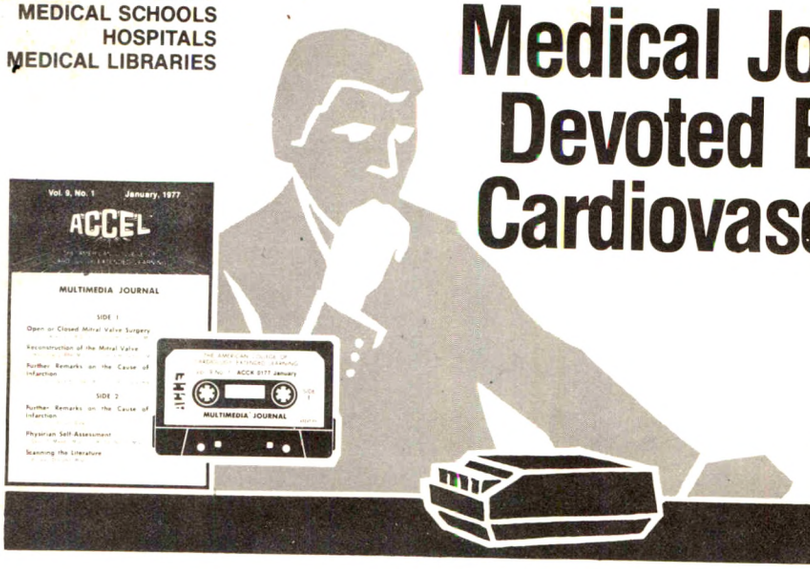

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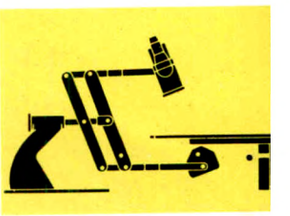

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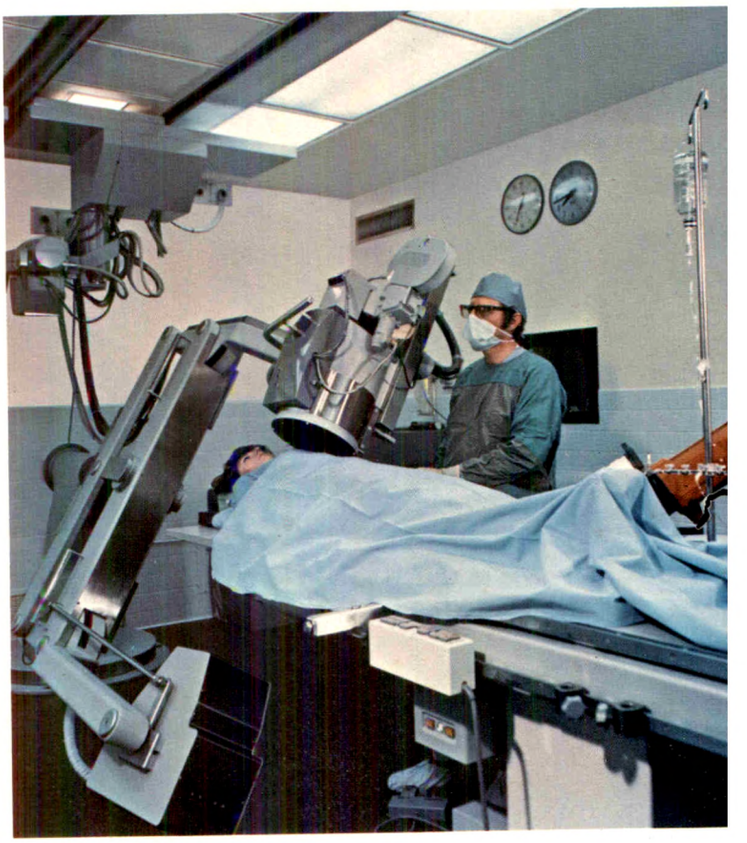

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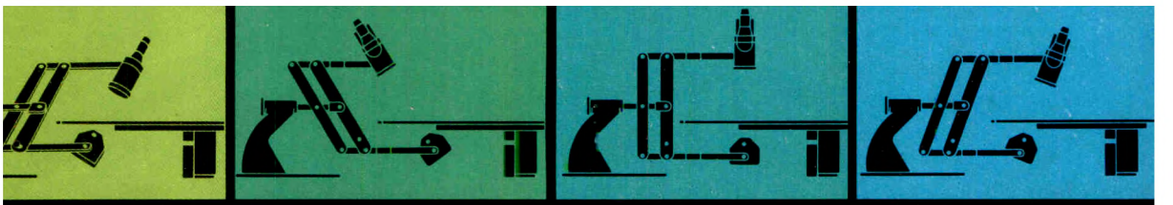

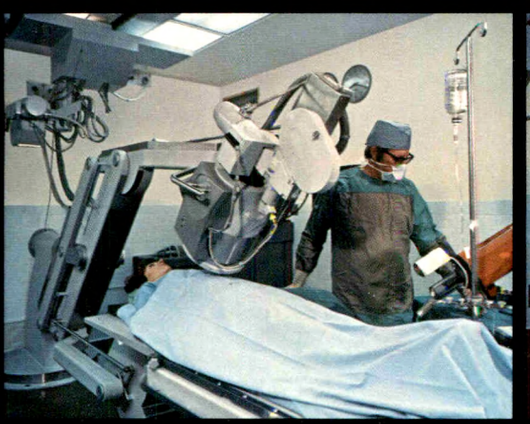

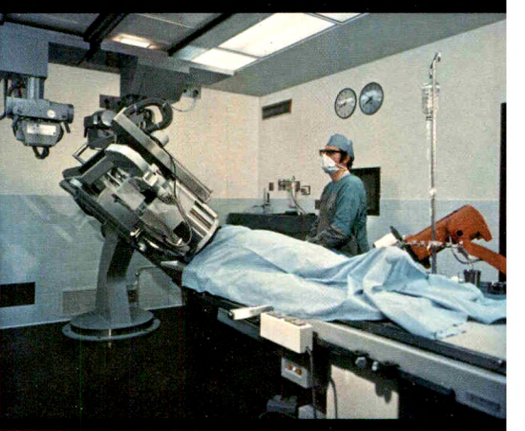

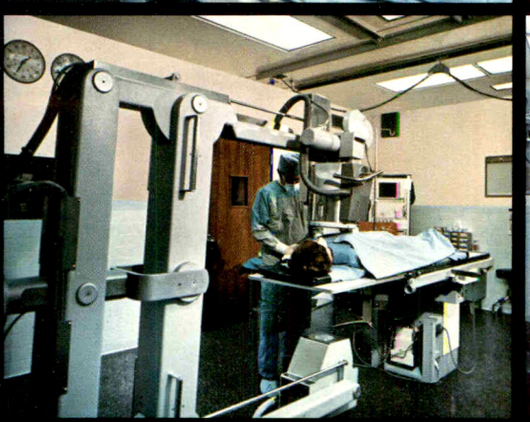

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Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

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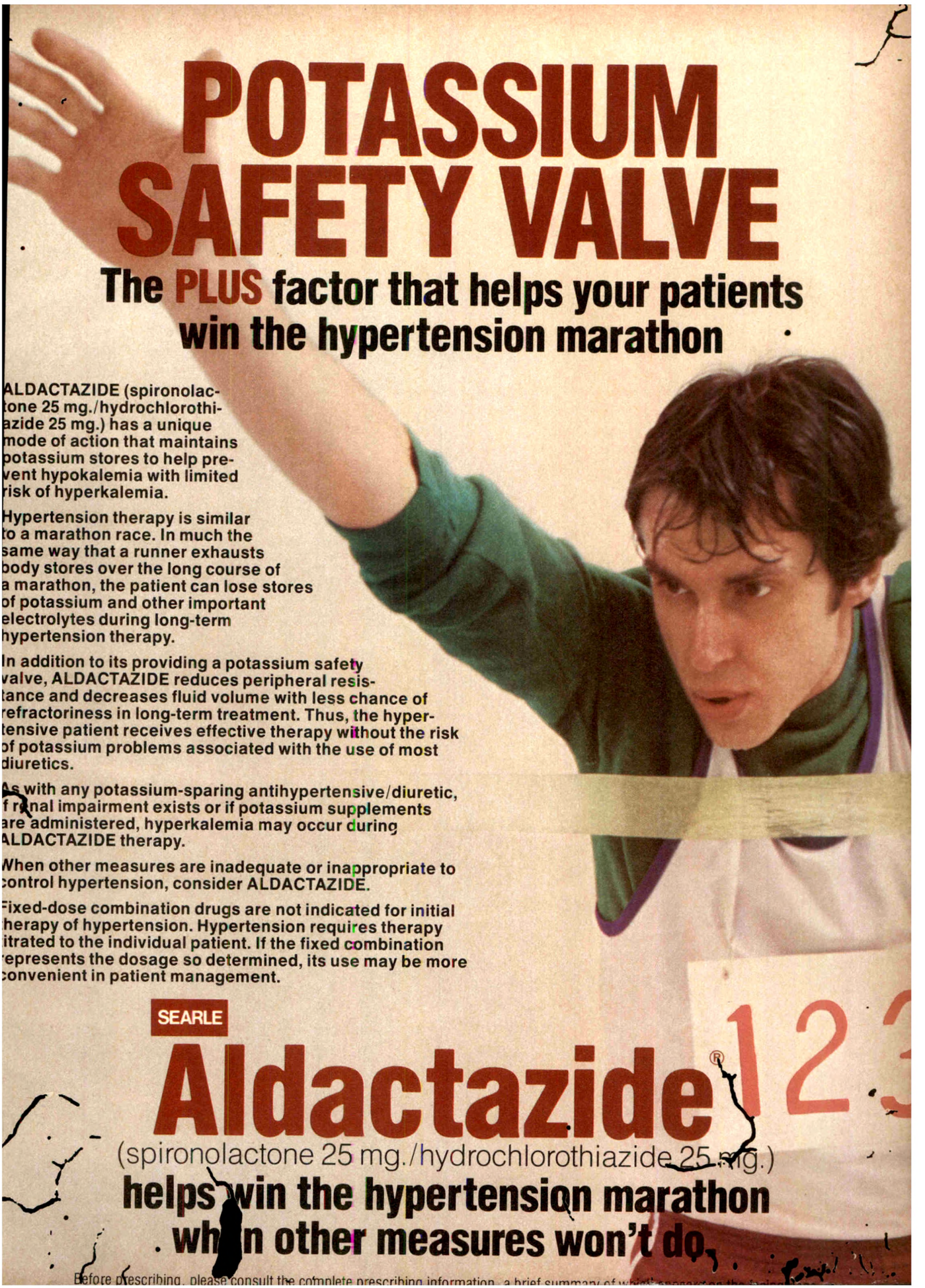

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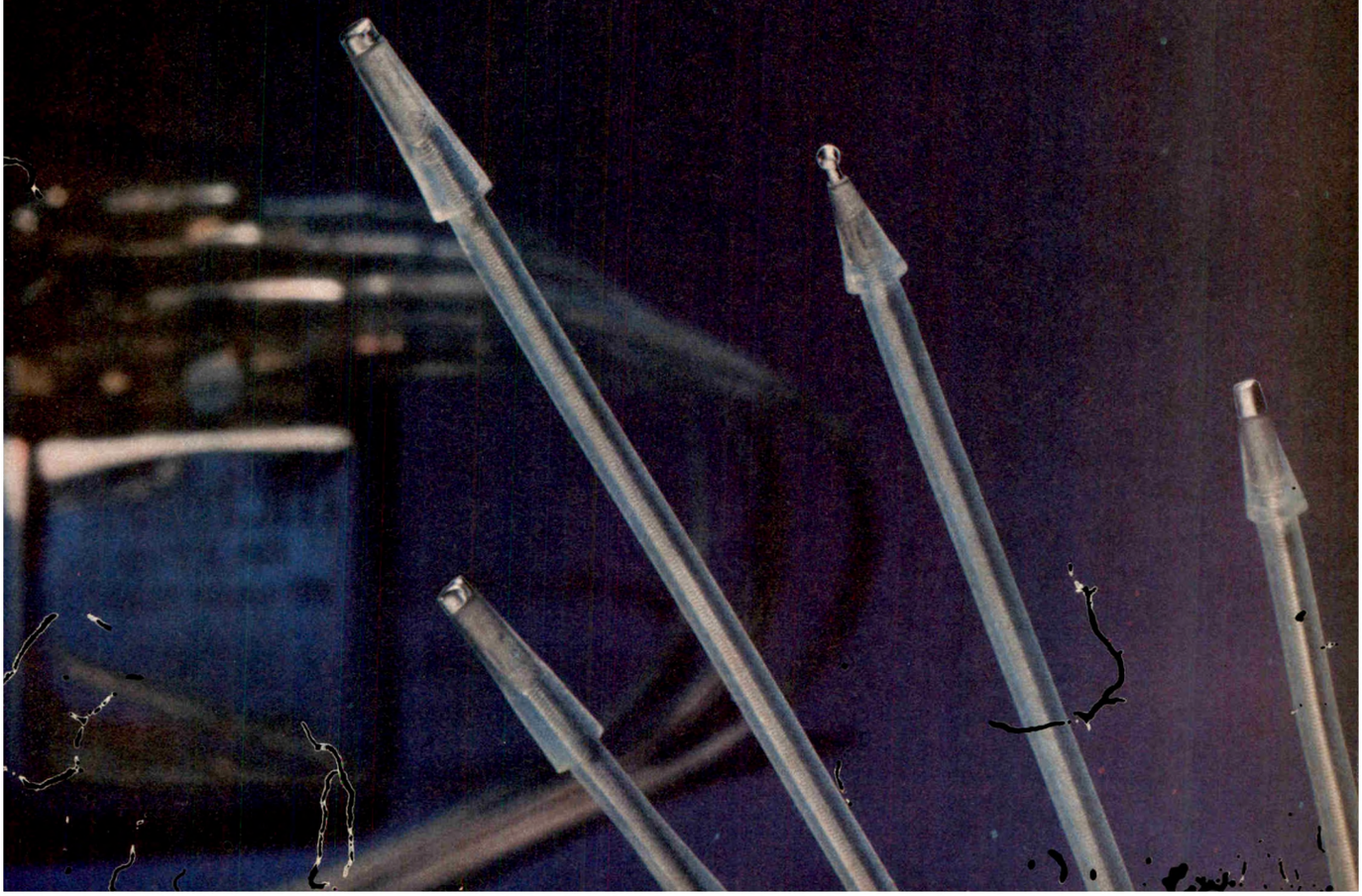

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Investigators have attributed the improvement to vasodilating effects of exercise, increased venous return and development of the collateral circulation. It is clear that exercise produces a tolerance for more exercise, and a program of regular walking, in the absence of any contraindications, appears to be an appropriate measure in the management of Peripheral Vascular Disease.

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Patients often compensate for claudication in calf muscles by adopting a shuffling gait. This "shuffling" utilizes calf muscles only minimally.

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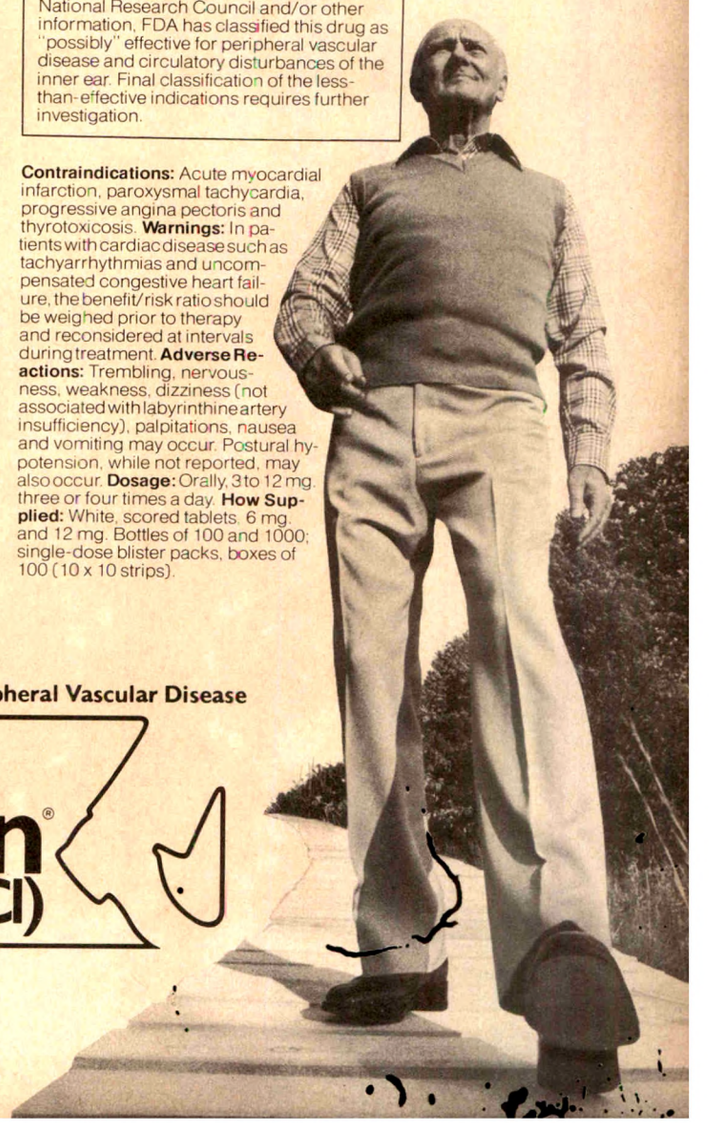

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†A bibliography of published papers on therapeutic walking is available upon request.

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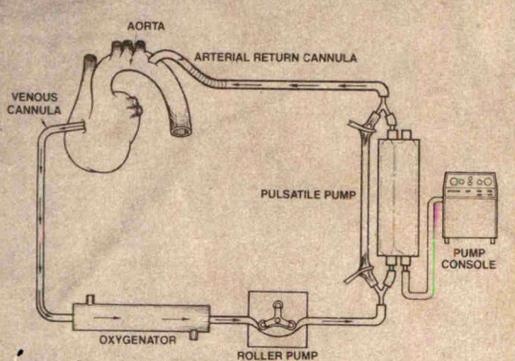

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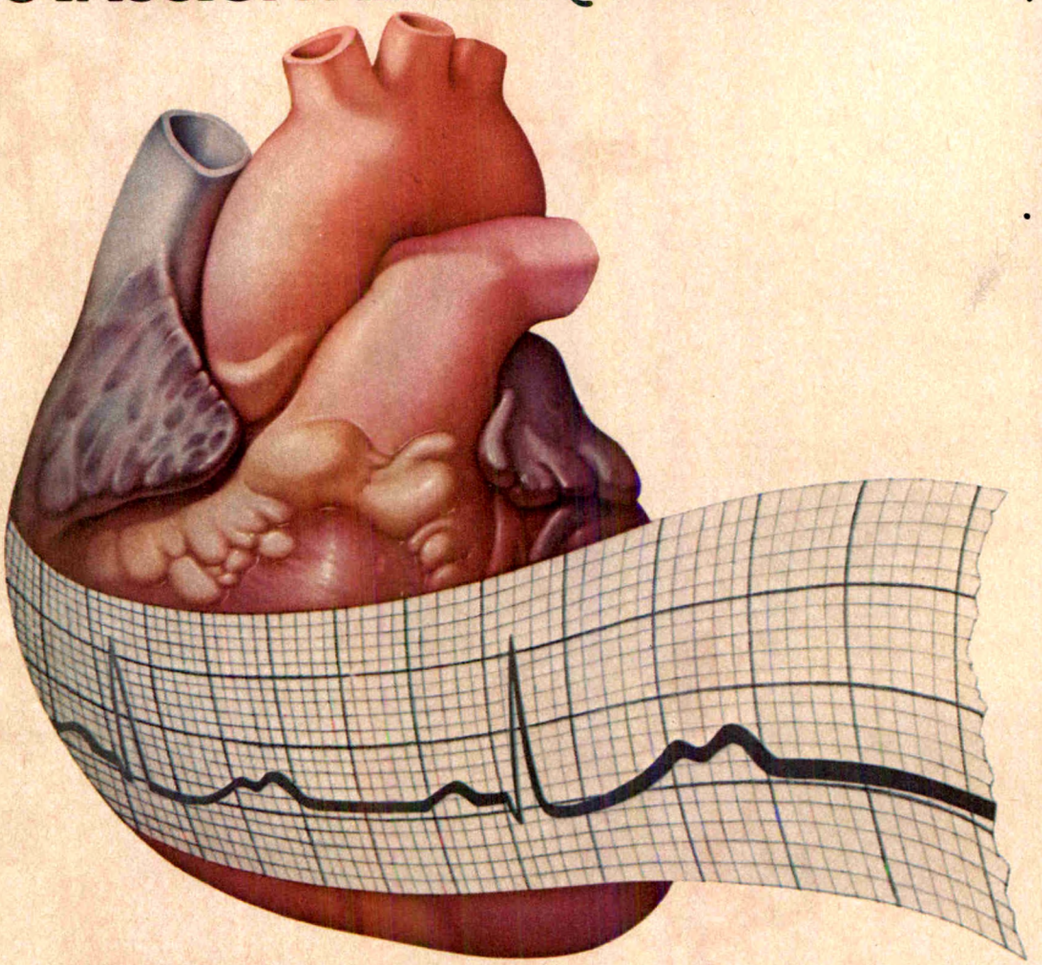

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Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: Nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effect is hyperkalemia (see Contraindications, Warnings and Overdosage).

Overdosage: If excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes. Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

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LETTERS TO THE EDITOR

CARDIOGENIC SHOCK IN THE CORONARY CARE UNIT

In the interchange between Stein and Flood and Kuhn[1] on intraaortic balloon pumping in acute myocardial infarction, Kuhn reports a 4.2 percent incidence rate of cardiogenic shock among patients admitted to the coronary care unit of Mt. Sinai Hospital in New York City. He suggests that this rate was low in comparison with that of the community hospital described by Stein and Flood because of better therapy, which prevented cardiogenic shock. Another possible explanation is that the community hospital is presented with more seriously ill patients because of factors in patient selection. Accordingly, we surveyed admissions to the coronary care unit of Jewish Memorial Hospital in New York in order to identify the percent of patients with acute myocardial infarction who already had cardiogenic shock when they arrived in the emergency room. This institution is a community hospital of 200 beds with an active outpatient department, emergency room and intensive coronary care unit (such as specified by Stein and Flood) and receives patients through the Emergency Police Ambulance System of New York City.

During 1976, a total of 107 patients with acute transmural myocardial infarction were admitted to the coronary care unit. Of this group, five patients already had cardiogenic shock when seen in the emergency room. These patients all demonstrated profound hypotension, cyanosis, cold skin and other signs and all died within a short time (3, 1.5, 2, 10 and 48 hours, respectively). None of these patients showed serious arrhythmias at the time of shock. Our incidence rate of cardiogenic shock at entry to the coronary care unit was thus 4.7 percent, which is equivalent to the total incidence rate at Mt. Sinai Hospital. In addition, five patients experienced cardiogenic shock while in the coronary care unit and died, and two others survived. Thus, the total incidence rate was 11.2 percent.

Does this finding demonstrate that coronary care units see different types of patients, perhaps depending on their geographic location and admitting procedures? We wonder whether our experience is common or unique and whether the incidence of patients who already have cardiogenic shock on arrival at the hospital is not a good index of the general severity of cases seen.

Richard P. Lasser, MD
Hwang Nam Chang, MD
Jewish Memorial Hospital
New York, New York

Reference

1. **Stein MF, Flood FB, Kuhn LA:** Intraaortic balloon pumping in acute myocardial infarction. Am J Cardiol 38: 668–669, 1976

REPLY

I agree that there may be some differences in the incidence of shock after acute myocardial infarction among different hospitals, possibly depending upon whether or not the hospital provides ambulance service.

Our data were based only on patients admitted to the coronary care unit. There may well have been additional patients who were moribund on entry to the emergency room who did not survive long enough to be admitted to the unit. Because Jewish Memorial Hospital receives patients through the Police Emergency Ambulance System, some of their patients may arrive at an earlier time after infarction and thus might survive to be admitted to the coronary care unit. However, this factor probably accounts for relatively few patients because studies have shown little difference in interval between onset of chest pain and arrival at the hospital between patients who experience shock after infarction and those who do not (about 6 hours in a voluntary hospital in New York City not served by a police ambulance system). An average of about 22 hours elapsed between the presumed onset of infarction and development of shock. It is difficult to compare precisely the Mt. Sinai data with those of Lasser and Chang because the latter studied a much smaller group of patients. I am not sure that there is a statistically significant difference between the two groups.

I did not compare our incidence rate of shock with that of Stein and Flood because they did not provide such information in their letter. The point I tried to emphasize was that the incidence of shock has declined in our own experience, a finding I attribute to more aggressive and effective management of pre-shock conditions that might predispose to the development of shock in some patients, such as heart failure, arrhythmias and respiratory and metabolic disorders. Unfortunately, this leaves a residual group of patients with extensive myocardial dysfunction who are, for the most part, refractory to medical management. The prognosis in patients with severe congestive heart failure without marked hypotension after acute myocardial infarction is much better than that of patients with cardiogenic shock, reasonably rigidly defined. Much of the reported efficacy of therapeutic interventions in "cardiogenic shock" may well be in this group of patients with heart failure without profound hypotension who have a more benign course with conventional management than do patients with profound hypotension. Regrettably, the patients with shock appear to be refractory to intraaortic balloon pumping and emergency revascularization surgery (unless there is surgically remediable ventricular septal defect or mitral regurgitation). I think it is clear that because of the very poor results with all forms of therapy once the shock state has occurred major efforts should be expended in identifying and classifying as to prognosis and appropriate therapy patients in a "pre-shock" group.

Leslie A. Kuhn, MD, FACC
Mount Sinai School of Medicine
New York, New York

SUBCLAVIAN APPROACH FOR CARDIAC CATHETERIZATION WITH BALLOON-TIPPED PULMONARY ARTERIAL CATHETER

For the past 2 1/2 years I have used a technique quite similar to that of Nadjmabadi et al.[1] Most of these procedures have been performed through the right subclavian vein. I agree that this technique is generally quite safe and time-saving. However, in two patients the subclavian artery was entered with the introducing needle. Each time hemostasis was obtained by local pressure over the site of puncture. In one of these patients, it was not possible to cannulate the subclavian vein on the initial side, possibly because of displacement of the vein by hematoma. Subclavian entry was easily done from the other

side. In a third patient a small (less than 10 percent) pneumothorax developed and resolved spontaneously over the next 12 hours. In a fourth patient, it was impossible to cannulate either the right or left subclavian vein.

Because of these complications, I believe that the subclavian approach is relatively contraindicated in patients who have disorders of hemostasis or are on a positive pressure respirator. In patients with disorders of hemostasis a cut-down procedure should be performed or the subclavian approach used with extreme caution. In patients on positive pressure respirators either the internal jugular femoral or antecubital vein should be used. A chest X-ray film should be obtained routinely immediately after the procedure to evaluate for possible pneumothorax.

Thomas M. Brown, Jr., MD
Des Moines, Iowa

Reference

1. **Nadjmabadi MH, Rastan H:** Subclavian approach for cardiac catheterization with balloon-tipped pulmonary arterial catheter. Am J Cardiol 39:471–472, 1977

REPLY

I appreciate the comments and the opportunity to add several other points.

Using Aubaniac's approach, we placed central venous catheters in more than 2,000 patients before using the Swan-Ganz catheter in the subclavian vein. The left subclavian vein provided easier entry into the pulmonary artery because of the special curve of the catheter-tip. The right pulmonary artery was easily entered from the left subclavian vein approach in more than 80 percent of our patients.

An 18 gauge needle is used for puncturing the vein and then Seldinger's technique is followed for placement of the catheter. Also, the positive end-expiratory pressure mechanism of the ventilator is turned off at the time the vein is punctured. These measures avoid the complications of pneumothorax and hematoma. If the prothrombin time is less than 10 percent of normal we do not attempt this procedure. To date we have used this technique in 115 patients and have found no occurrence of bleeding or pneumothorax. Others[1] report an 8.8 percent incidence rate of these complications with internal jugular vein puncture.

Mohammed H. Nadjmabadi, MD
Intensive Care Unit
Queen Pahlavi Foundation
Cardio-Vascular Medical Centre
Tehran, Iran

Reference

1. **Loers FJ:** Klinische Erfahrungen dem Kavakatheter ueber die Ven Jugularis interna. Prakt Anaethesie 11:28–30, 1976

ANOMALOUS LEFT CORONARY ARTERY

I wouldn't want to accuse Grace et al.[1] of being male chauvinists since I don't know their gender, but they incorrectly credit Brooks[2] with the first description of the origin of the left coronary artery from the pulmonary artery. Although Brooks was the first to report anomalous origin of the coronary arteries, in his two cases both patients had anomalous *right* coronary artery. The first description of anomalous left coronary artery was by Maude Abbott[3] in 1908.

Glen G. Cayler, MD
Sacramento, California

References

1. **Grace RR, Angelini P, Cooley DA:** Aortic implantation of anomalous left coronary artery arising from pulmonary artery. Am J Cardiol 39:608–613, 1977
2. **Brooks HJ:** Two cases of an abnormal coronary artery of the heart arising from the pulmonary artery. Gen Anat Physiol 20:26, 1886
3. **Abbott ME:** Congenital cardiac disease. In, Osler's Modern Medicine, Vol 4. Philadelphia, Lea & Febiger, 1908, p 420

REPLY

Frankly, we have not been able to locate the reference by Brooks. However, our information came from Abbott's chapter in "Osler's Modern Medicine." In her description it is difficult to be certain whether the cases described by Brooks were of actual anomalous origin of the coronary artery from the pulmonary artery or a type of cirsoid formation of vessels on the main pulmonary arterial trunk just above the valve. We have seen eight such cases in which the coronary orifices arose normally from the aortic surfaces but yet a left to right shunt was present with angiomatous vessels from the left anterior descending or, in one case, from both the left and right coronary arteries. That lesion produces a coronary steal phenomenon and may cause angina in adult life but seldom during infancy or childhood. In Abbott's account she states:

> Anomalous Origin from the Pulmonary Artery.—In this a vessel arises from a sinus of Valsalva of the pulmonary artery, and, meeting the branches from the aortic coronaries, produces a remarkable anastomosis of a cirsoid character. Two such cases have been reported by Brooks and one by Krause, and a fourth, unique in several particulars, in the McGill Museum was destroyed by the recent fire.

Denton A. Cooley, MD, FACC
Texas Heart Institute
Houston, Texas

HISTORY OF CARDIAC PACING—I

Parsonnet's excellent review of cardiac pacing[1] erroneously credits me with the development of "external programming." My understanding of this development is as follows: Rate and amplitude adjustments were available in one of the early asynchronous pacers developed by Wilson Greatbatch. These adjustments required percutaneous insertion of a Keith needle. The obvious advantages and disadvantages prompted many persons to think about ways of making noninvasive adjustments on implanted pacers.

In the 1960's, D. E. Williamson designed and built a model of a three position magnet-activated implantable switch for "external programming." (I have a notebook entry from June 1970 on an externally rotated magnet that would turn an implanted variable resistor with another small magnet attached perpendicular to its shaft. The same idea was actively pursued by Medtronic engineers; mine stopped with a crude model.) However, the spark that started the development of the Omnicor system came from W. P. Murphy, Jr., who originally suggested this program and supported it throughout its development and its clinical use over the years. The invention of the Programming System is officially credited to Reese S. Terry, Jr. and Gomer L. Davies in U.S. Patent no. 3,805,796, entitled "Implantable Cardiac Pacer Having Adjustable Operating Parameters." The programming link is based on the rapid closing and opening of a dry reed switch by a pulsating magnetic field. My understanding is that the transmission method was suggested originally by V. T. Cutolo, Jr.

I was fortunate to work with all these gentlemen at the time, but I do not feel entitled to receive credit for external pacing.

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Reference

1. **Parsonnet V:** Permanent pacing of the heart. Am J Cardiol 39:250–256, 1977

HISTORY OF CARDIAC PACING—II

William Chardack has written me concerning a few erroneous references in my review of permanent pacing:

In 1959 Hunter and his colleagues[1] did implant the first myocardial electrode, not the first pacemaker. Chardack et al.[2] reported the first pacemaker implantation in 1959.

The first engineering work on pacemakers by Greatbatch[3] was actually done in 1958, not in 1959 as indicated in Table III.

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MYOCARDIAL RUPTURE

Raizes et al.,[1] writing of "instantaneous nonarrhythmic death" in acute myocardial infarction, use this designation for the sudden cessation of all signs of mechanical activity of the heart although sinus rhythm, as assessed with the electrocardiogram, was maintained for some time.

This syndrome, generally named electromechanical dissociation (although we consider electrohemodynamic dissociation a more proper term), is usually ascribed to a cardiac rupture.[2–5] It is surprising that none of the seven patients meeting this criteria at autopsy had cardiac rupture. In addition, the authors state that the three cases of rupture recorded in 10 years did not meet the criteria for this syndrome.

Our personal data are just in opposition to these findings. In an 8 year experience in our coronary care unit, we followed up 2,032 cases of acute transmural infarction in which the total mortality rate was 14 percent. We recorded 31 cases of death in patients with electrohemodynamic dissociation, with 19 necropsy examinations. In all cases the heart manifested rupture of the free wall of the ventricle that occurred in the first 3 days of infarction in all but three cases. All patients were in classes I and II of the Killip classification, and most were more than 60 years old and female.

In light of these two separate groups of patients, we wonder if a more detailed analysis of the terminal electrocardiogram would help to differentiate these mechanisms of death.

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5. **Penther P, Hemon P, Blanc JJ, et al:** Les ruptures du coeur à la phase aiguë de l'infarctus du Myocarde. Arch Mal Coeur 68:711–718, 1975

REPLY

The anatomic observation of myocardial rupture in all 19 cases in Dr. Cordeiro's series is indeed remarkable. We had expected to find rupture in our patients and were surprised when it was not present. We suspect that it was only by chance that no cases of rupture were included in the seven that were studied. It would be important to know the specific findings that were termed "rupture" in Cordeiro's series. Was percardial tamponade found in all patients? If not, was rupture really the cause of death in these patients? Could the evidence of a rupture have been produced post mortem during attempts at resuscitation? The term "electrohemodynamic dissociation" would indeed be preferable to "electromechanical dissociation" because the generation of some cardiac pumping capability has been demonstrated in some of these instances.[1]

It would be important to obtain full 12 lead electrocardiograms at the time of occurrence of this phenomenon. This might provide insight concerning etiology.

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Reference

1. **Caulfield JB, Zir L, Harthorne JW:** Blood calcium levels in the presence of arteriographic contrast material. Circulation 52:119–123, 1974

COMMENT

I am glad to provide further information about our 19 cases of cardiac rupture.

In our experience rupture of the free wall results from an intramural dissection, usually a sinuous, multichannel hematoma, beginning with an endocardial tear and ending in single or multiple lacerated openings in the epicardium.

There was a large amount of blood and clotting in the pericardial cavity in all cases. Cardiac massage was not attempted in any case. In three cases we tried unsuccessfully to decompress the tamponade by pericardiocentesis. Reference 4 describes our early cases. Succeeding cases confirmed these observations.

Arsenio Cordeiro, MD, FACC

ECHOCARDIOGRAM IN MITRAL STENOSIS

Parisi et al.[1] state that there have been no published prospective series evaluating the accuracy of M mode scans in grading the severity of mitral stenosis. I therefore draw the authors' attention to a prospective study[2] in 26 patients evaluating the accuracy of conventional echocardiography in predicting the degree of mitral stenosis and pliability of valve

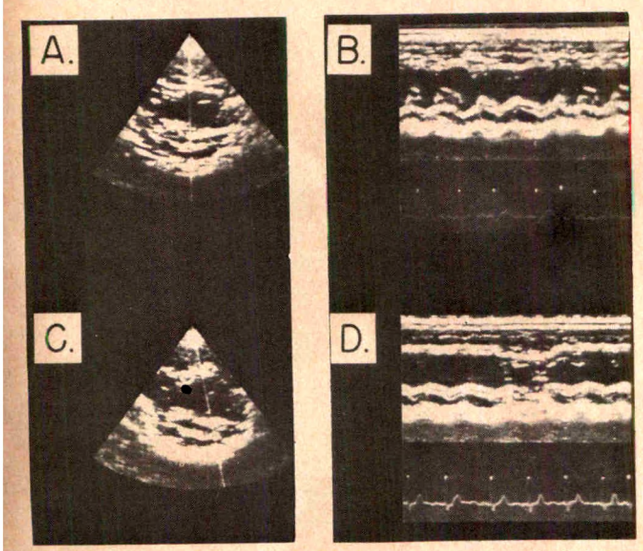

FIGURE 1. Two dimensional cross-sectional and M mode views of a stenotic mitral valve. **A and C,** diastolic cross-sectional views of the mitral orifice made with a phased array sector scanner. The radii **(white lines)** indicate the direction of a single beam for the M mode display. In **C** the radius is near the commissure rather than at the center of the stenotic orifice. **B,** M mode record made along the beam directed through the center of the mitral orifice as indicated in **A; D,** M mode accord from the radius shown in **C.** The E-F slope and valve excursion are less in **D** than in **B.**

leaflets when compared with cardiac catheterization data and measurements made at open commissurotomy.

Echocardiographic categorization of mitral stenosis as severe (E-F slope 15 mm/sec), moderate (15 to 25 mm/sec) or mild (25 to 35 mm/sec) was compared with estimates of the mitral valve area as calculated with the Gorlin formula and measured with calibrated probes at surgery: (severe <0.5 cm^2, moderate 0.5 to 1.00 cm^2 and mild 1.00 to 1.5 cm^2). In 15 patients there was agreement between the echocardiographic and surgical estimate of the severity of mitral stenosis; in the remaining 11 patients the echocardiogram indicated greater stenosis than was found at surgery. Among the 21 patients whose valve area was calculated with the Gorlin formula, there was agreement in 6 between the echocardiographic and the Gorlin estimates of the severity of mitral stenosis; in 13 the echocardiogram indicated greater stenosis than the Gorlin formula, and in 2 the reverse was true. In the latter two patients the echocardiographic and surgical assessments of the severity of stenosis were in agreement. The presence of a low cardiac index, atrial fibrillation and mitral regurgitation did not significantly contribute to these relations.

Surgical assessment of impaired pliability was related to anterior mitral leaflet excursion of less than 20 mm and less than 15 mm. Ten of 14 patients considered to have impaired pliability at surgery had anterior leaflet excursions of less than 20 mm. One with pliable leaflets had an anterior leaflet excursion of less than 20 mm ($P < 0.01$). No patient with a normal pliability had an anterior leaflet excursion of less than 15 mm; 4 of 14 patients with impaired pliability had anterior leaflet excursion of less than 15 mm ($P < 0.05$).

These data suggest that the severity of mitral stenosis is overestimated by current criteria and that anterior leaflet excursion of less than 20 mm is a more sensitive indicator of impaired pliability than anterior leaflet excursion of less than 15 mm.

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REPLY

We agree that the severity of mitral stenosis cannot be accurately determined in a large series of patients using the E-F slope as an index of severity. Many have found this to be the case. Of interest is the evolving disenchantment that echocardiographers have had about this measurement in mitral stenosis over the past decade. Yet, in the original studies of Gustafson et al.,[1] the correlation coefficient between E-F slopes and other objective assessments of the severity of mitral stenosis is not much different from that reported in recent series.[2,3] Several current studies[4–6] have indicated that two dimensional echocardiography is the preferred means of assessing the severity of mitral valve stenosis because the orifice can be directly imaged with a cross-sectional approach and its area determined with planimetry.

Perusal of Figure 1 suggests a possible explanation of the tendency of conventional M mode techniques to overestimate the severity of mitral stenosis. The anterior mitral leaflet in mitral stenosis often has its greatest excursion at the widest portion of the stenotic orifice area. As the eye moves toward the edges of the orifice there is less anterior motion, a slower E-F slope and poorer leaflet separation. Thus, in many instances standard M mode echocardiography will overestimate the severity of mitral stenosis because there is no assurance that the widest portion of the orifice or the area of greatest mobility of the anterior leaflet has been traversed.

Horgan's comments regarding the pliability of mitral valve are interesting. Pliability is a subjective end point, and judgments about it may vary considerably from surgeon to surgeon. Hence, it is a characteristic that may be very difficult to assess from one study to another.

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CUSP SEPARATION IN AORTIC STENOSIS

I am in disagreement with the conclusions of Chang et al.[1] that measurements of mid-systolic cusp separation are invalid as an index of the severity of aortic stenosis. However, I agree that cusp deformity should and does preclude an exact correlation between echocardiographic cusp separation and severity of aortic stenosis. Nevertheless, a number of studies and our own experience suggest that, when separation of *clearly defined* cusps is less than 15 mm, hemodynamic aortic stenosis

is present. In this sense, echocardiography is a useful tool in screening systolic ejection murmurs for possible cardiac catheterization.

From Table I, I note that 13 of 14 patients with apparent mid-systolic aortic cusp separation of 15 mm or less and with cardiac catheterization had a significant gradient across the aortic valve or significantly reduced aortic valve area. The one discrepancy was Patient 1 in whom apparent mid-systolic aortic cusp separation was reported at a maximum of 13 mm. In Figure 1 from Case 1, I measure an 18 mm cusp separation in the complex labeled number 3.

I am also disturbed by two other facets of the study. First, the authors do not report the interobserver and intraobserver reproducibility of the measurement of aortic separation. Clearly, this measurement is subjective to a certain extent. For example, in Figures 3 and 4, I would have measured aortic cusp separations as significantly less than the authors' **arrows** indicate. Second, every patient in this series except the first had significant aortic stenosis. Thus, there is no control group of patients with a normal aortic valve or a diseased aortic valve without stenosis with which to test the hypothesis that aortic cusp separation does detect aortic stenosis.

I remain convinced that if one is careful to measure cusp separation only in situations where cusp echoes are clearly identified (for example not Figure 5 and probably not Figure 2) and if one does not expect exact correlation between cusp separation and aortic valve orifice, the echocardiographic examination of aortic cusp separation does provide useful clinical information. Particularly, cusp separation of less than 15 mm appears to have a relatively high level of sensitivity and specificity for hemodynamic aortic stenosis. However, like any other laboratory examination, these findings must be correlated with other clinical and laboratory data available on the patient.

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Reference

1. **Chang S, Clements S, Chang J:** Aortic stenosis: echocardiographic cusp separation and surgical description of aortic stenosis. Am J Cardiol 39:499–504, 1977

REPLY

It is interesting that Hammermeister would disregard the echocardiogram of every patient with suspected aortic stenosis if the cusp separation was not "clearly defined." Picture book clarity is not the goal. As he indicates, the echocardiogram was a useful screening method to identify abnormal aortic valve motion in patients who had clinical symptoms of syncope, heart failure, systolic ejection murmur or chest pain. We did not appreciate the *clinical severity* of the aortic stenosis from the echocardiogram. Cases 3, 4, 7, 9, 10, 13 and 14 did not have evidence of left ventricular hypertrophy in the echocardiogram, angiogram or electrocardiogram or at surgery. Yet they all had an abnormal aortic valve echocardiogram and a gradient exceeding 45 mm Hg. This agrees with Hammermeister's premise that reduced cusp separation indicates severity of obstruction. However, Cases 3, 8, 16, 20 and 22 exhibited apparent systolic cusp separation of 15 mm or greater; these patients also exhibited hemodynamically significant aortic stenosis. The point is that in each patient there was so much variation in cusp separation, secondary to transducer position, respiratory changes, systolic displacement of the aortic root and manipulation of instrumentation, one could not definitely say which cusp separation in the tracing was truly representative of the severity of the obstruction. Variations in interobserver and intraobserver measurements were meaningless.

The arrows in the illustrations, with the exception of those in Figure 2, demonstrate leaflet tissue motion selected as representative of the variety of cusp motion. The illustrations were not meant to be precise areas from which the measurements in Table I were derived.

We believed that inclusion of echocardiograms and discussion of normal aortic cusp separation and congenital bicuspid aortic stenosis would have been redundant. Ample study of normal and congenital bicuspid aortic valve motion can be found in published studies.[1–10]

We continue to support the conclusions presented in our article. The echocardiogram was useful to detect underlying aortic disease, but clinical severity of the obstruction was based on the patient's history, physical examination and cardiac catheterization.

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LEFT VENTRICULAR COMPLIANCE

Gaasch et al.[1] report that an index of end-diastolic distensibility (dV/dP), defined as the inverse slope of a tangent to the pressure-volume curve at end-diastole, may be calculated as:

$$dV/dP_{ed'} = 1/k'P$$

and that end-diastolic volume compliance, likewise may be calculated as $(dV/dP)_{ed'}$ normalized for end-diastolic volume:

$$(dV/VdP)_{ed'} = 1/K'P \cdot 1/V$$

where P = end-diastolic pressure, V = end-diastolic volume and k′ = the slope of ln P-V relation obtained by the double coordinate method.

They add that another method of evaluating left ventricular diastolic volume compliance utilizes a single coordinate of end-diastolic pressure and volume and a constant pressure intercept (b) of 0.43 mm Hg. This method assumes that the end-diastolic pressure-volume relation can be represented as:

$$\ln P = kV + \ln 0.43.$$

This equation can be rearranged and rewritten as:

$$K = (\ln P - \ln 0.43)/V.$$

Because the values for the slope of the ln P-V relation are similar by the single and double coordinate methods, they conclude that estimates of end-diastolic compliance would likewise be little changed if the simplified (single pressure-volume coordinate) method of obtaining $(dV/VdP)_{ed}$ were used in place of the multiplied coordinate approach. Therefore, because left ventricular $(dV/VdP)_{ed}$ may be calculated as:

$$(dV/VdP)_{ed} = 1/kP \cdot 1/V,$$

we point out that assuming

$$K = (\ln P - \ln 0.43)/V,$$

it derives that

$$(dV/VdP)_{ed} = \frac{1}{\frac{(\ln P - \ln 0.43)}{V} \cdot P} \cdot \frac{1}{V},$$

and simplifying for V,

$$(dV/VdP)_{ed} = \frac{1}{(\ln P - \ln 0.43) \cdot P}$$

Thus P becomes the only determinant of $(dV/VdP)_{ed}$ and V is not considered. In fact, in the paper of Gaasch et al., all the patients with the same left ventricular end-diastolic pressure have identical values of (dV/VdP) (for example, when left ventricular end-diastolic pressure = 11 mm Hg, (dV/VdP) = $2.8 \cdot 10^{-2}$/mm Hg for Patients 1, 3 and 8 in spite of different values of end-diastolic volume). Because left ventricular end-diastolic pressure not only is an expression of left ventricular end-diastolic compliance but also is an index of left ventricular insufficiency, we think that this mathematical joke has no clinical meaning.

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Reference

1. **Gaasch WH, Quinones MA, Waisser E, et al:** Diastolic compliance of the left ventricle in man. Am J Cardiol 36:193–201, 1975

REPLY

In an analysis of length-performance relations in diseased ventricles of varying dimensions and compliance, we utilized left ventricular end-diastolic distensibility (dV/dP), normalized for end-diastolic volume (dV/VdP), as an index of muscle parallel elasticity.[1,2] The rationale for this normalization rested in the difference between the distensibility of the left ventricle as a chamber and the distensibility of a unit volume of myocardium. If one considers an adult's heart and a child's heart, both with normal myocardium, dV/dP is lower in the child's heart than in the adult's heart, in part by virtue of the smaller operating volume of the child's heart. The distinction between chamber and muscle distensibility is of critical importance in any discussion of the diastolic properties of the left ventricle.

The limitations of these early studies are well known,[3,4] and the observation made by Fantini and Michelucci has been discussed by Covell and Ross.[5] To a great extent, the basis of these limitations originates in the calculation of left ventricular compliance from a single end-diastolic coordinate of pressure and volume and an assumed fixed (zero volume) pressure intercept. These oversimplifications were necessary before we were able to measure accurately diastolic pressure and volume throughout diastole; however, with the availability of angiographic catheters with distally mounted micromanometers, we now analyze our clinical data in terms of chamber compliance (pressure-volume data) and myocardial stiffness (muscle stress-strain data).[4,6,7] Our current nomenclature and methodology are outlined in a recent article in this Journal.[4]

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ELECTROCARDIOGRAPHIC LEFT ATRIAL ENLARGEMENT VERSUS INTERATRIAL CONDUCTION DEFECT

Josephson et al.[1] suggest that the term left atrial enlargement should be replaced by interatrial conduction defect. We used this term in 1976.[2] Employing high gain vectorcardiography, X-ray films and echocardiography, we concluded that "one cannot assess with certitude the separate contribution made by conduction delay and hypertrophy or dilatation to the enlargement of PsE loop." In many patients "the posteroanterior ratio of the P loop in the horizontal plane was increased in spite of a normal size left atrium." It is well known that the large posteriorly oriented P loop corresponds to the wide and deep negative terminal deflection of P waves recorded in lead V_1 of the conventional electrocardiogram.

Josephson et al. confirmed our findings when they concluded that the "electrocardiographic pattern termed left atrial enlargement appears to represent an interatrial conduction defect that can be produced by a variety of factors." Follow-up studies using electrocardiography,[3] vectorcardi-

ography[4] and echocardiography in 89 normotensive diabetic patients with no apparent cardiac disease revealed in 22 patients P wave abnormalities caused by conduction disturbances. The left atrium was enlarged in only three patients. This latest finding suggests the need for more caution in ruling out left atrial enlargement in the presence of abnormal duration and contour of the P wave. In opposition to Josephson et al., we believe that the term intraatrial conduction disturbance must not be loosely used because both such disturbance and enlargement of the left atrium may be present. For all practical purposes, the X-ray film and echocardiography may be helpful in differentiating an enlarged left atrium from a normal-sized atrium with intraatrial conduction disturbances.

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REPLY

Basically Zoneraich and Zoneraich agree with our conclusions but offer a caution that one may have only atrial enlargement producing P wave abnormalities in the absence of prolonged intraatrial conduction. We disagree with their caution in that prolongation of the P wave (one of our criteria for electrocardiographic "left atrial enlargement") by definition means that atrial activation time is prolonged. Thus, it is inconceivable that, in the presence of a prolonged P wave, the P loops could be normal in duration, a variable not evaluated in the paper cited in Reference 2 of Zoneraich and Zoneraich. In that paper there is no category for prolonged P loop duration in the absence of notching.

In our study we used atrial endocardial mapping to analyze the role of left atrial pressure or volume overload and interatrial conduction in the genesis of electrocardiographic "left atrial enlargement." Our conclusions were only meant to imply that prolongation of interatrial conduction is the common denominator of the electrocardiographic abnormality termed left atrial enlargement. As we stated, delayed left atrial activation can be produced by several factors, one of which is left atrial enlargement. However, as we also noted, the mere presence of left atrial enlargement does not necessarily imply a causal effect on atrial activation because the underlying atrial disease (rheumatic disease, ischemia, for example) may be the cause of the delayed atrial activation whereas the enlarged left atrium is an epiphenomenon.

We believe that in the absence of direct measurement of atrial conduction *velocity*, vectorcardiography may be of value in separating delayed activation due to an impulse traveling along pathway at a normal conduction velocity (smooth, evenly inscribed P loop) versus an impulse which may conduct slowly through a normal or long pathway (slowly inscribed and notched P loop).

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ABNORMAL SEPTAL MOTION AFTER CORONARY BYPASS SURGERY

Righetti et al.[1] found abnormal septal motion early after coronary bypass operations. Their report surprised me with its extremely small incidence (3 of 40 cases) of preoperative septal asynergy in patients undergoing graft surgery for obstruction of the left anterior descending coronary artery. Jacobs et al.[2] noted septal asynergy in 30 of 38 cases with significant occlusion of this artery. In our echocardiographic laboratory, abnormal septal motion occurred in 34 of 55 patients with significant occlusion of this artery and it occurred only slightly more frequently (29 of 41 cases) in patients who had had a previous myocardial infarction as well.

The authors concluded that abnormalities in postoperative septal movement may be reversible in some cases. Our experience fully supports their data. Among 19 patients undergoing grafting to the left anterior descending coronary artery, interventricular septal asynergy occurred in 13 patients preoperatively and in 17 patients 3 to 4 weeks after operation. At late follow-up examination (12 to 16 months after operation) abnormal septal motion was noted in only six patients. Early postoperative coronary angiography did not reveal graft occlusion in patients with abnormal septal motion. Two of three patients with perioperative infarction had early postoperative septal asynergy, but in one of them septal motion had reverted to normal at the 1 year follow-up study.

The authors suggest two possible mechanisms of abnormal postoperative septal motion: disruption of the pericardium and reduced myocardial performance of the interventricular septum. To test this assumption we analyzed our data on patients with aneurysmectomy. Pericardial disruption in this group should also have resulted in abnormal septal motion. However only one of five patients with normal preoperative septal motion was found to have abnormal septal motion after operation.

We conclude that pericardiotomy, perioperative infarction and early graft occlusion are not responsible for the early postoperative septal asynergy in patients with grafts to the left anterior descending coronary artery. Because such grafts are usually inserted into the mid or distal part of the vessel beyond the origin of the first septal branch, we suggest that in the early postoperative period blood flow in the septal perforating branches is reduced as a result of the Venturi effect caused by the high blood velocity in the graft.

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REPLY

On the basis of our echocardiographic data, which analyzed the amplitude of motion and thickening of the interventricular septum, we delineated two possible mechanisms for abnormal septal movement after coronary artery bypass graft surgery. The first, augmented anterior movement of the entire heart during systole because of pericardial disruption, is probably least important in coronary bypass surgery but explains why paradoxical septal motion can be seen with normal septal thickening as has been observed after pericardiectomy.[1] Why only one of Lengyel's five patients demonstrated abnormal septal movement after aneurysmectomy is not clear, especially since reversed septal motion is common after valve replacement surgery.[2] Perhaps aneurysmectomy distorts the geometric relation of the septum to the left ventricle.

The second and more important mechanism is reduced septal myocardial performance in the early postoperative period. The exact cause of this depressed function is unknown. We did not claim that the septum was infarcted in all of our patients with abnormal septal motion after coronary bypass surgery; in fact, we could confirm septal infarction in only one patient. Lengyel postulates that high blood flow velocity at the site of graft insertion in the mid left anterior descending coronary artery causes reduced flow in the more proximal septal perforating branches, which leads to early postoperative septal abnormalities. However, this theory does not explain why the septal abnormalities decrease late after operation in the majority of patients. Also, abnormal septal motion developed in two of our four patients with grafts to be proximal left anterior descending coronary artery.

We do not know why we had such a small incidence of abnormal septal movement preoperatively compared with the incidence in other series. However, Gordon and Kerber[3] recently found only a 46 percent incidence rate of septal abnormalities in a group of 26 patients with disease of the left anterior descending coronary artery. One possible explanation is that in almost all of our 37 patients with significant occlusion of this artery, the occlusion was located distal to the origin of the first septal perforating branch. Therefore, upper septal performance may have been fortuitously preserved in a larger number of our patients.

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INTERNAL MAMMARY ARTERY GRAFTS

Loop et al.[1] cite a patency rate for 261 internal mammary artery grafts of 95 percent, compare this with a patency rate of 86 percent for 1,208 saphenous vein grafts to the anterior descending coronary artery and indicate that this difference is statistically significant ($P < 0.002$). They also indicate that internal mammary artery grafts were usually not performed in patients over 65 years of age or in patients with extensive brachiocephalic atherosclerosis, unstable angina pectoris, "large" coronary arteries or left ventricular hypertrophy. Thus, statistical comparison of patency rates for internal mammary artery grafts, admittedly utilized in a selected group, to saphenous vein grafts inserted into the anterior descending system, does not appear warranted. One must assume that the "excluded patients" received saphenous vein grafts. The percent of patients in whom the internal mammary artery was not used for one of these reasons is not stated. In other reports, 3 to 7 percent of internal mammary grafts have been discarded for one of these or other reasons.[2–4] In addition, late stenosis of internal mammary grafts has been noted to occur in 5 to 11 percent of patients,[2–4] a higher incidence rate than for vein grafts.[3,5] If these figures are considered representative, then the incidence of "successful" internal mammary artery grafts declines to a value approaching that for saphenous vein grafts.[6] Loop et al. indicate that 831 internal mammary artery grafts have been restudied at the Cleveland Clinic, but the incidence of late stenosis in this group is not documented. Because comparable early and long-term results have been reported from other centers using saphenous vein grafts predominantly or exclusively, it would appear that the other factors cited by the authors (reduced operative mortality, reduced incidence of intraoperative infarction and more complete revascularization) are more important determinants of these improved results than use of the internal mammary artery.

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REPLY

Kouchoukos is correct to the extent that comparing patency rates of internal mammary artery grafts with saphenous vein grafts is imperfect because of considerations in selecting the arteries for grafting. We do not believe that selection factors are the major reason for the greater incidence of internal mammary artery graft patency. The comparison was made to highlight the higher patency rate of the internal mammary artery graft *despite* the frequently smaller size of the coronary vessels to which the graft was connected. The number of patients in whom the mobilized internal mammary artery was discarded has remained about 3 percent. Our experience indicates that usually this problem is technical and rarely related to atherosclerosis.

Our experience with stenosis of internal mammary artery grafts is cited in the article. In the entire series, only two patients who were restudied had stenotic graft anastomosis. We doubt that internal mammary artery anastomosis, properly performed, is associated with late anastomotic occlusion. Thus far, 27 patients have had more than one postoperative angiogram and none had a late stenosis.

In our entire experience through 1976, a total of 1,114 internal mammary artery grafts have been restudied after an average interval of 14 months; the patency rate is 96.2 percent. As stated clearly in the article, the improved survival in the series cannot be attributed solely to the internal mammary artery graft. Better criteria for patient selection, technical improvements, more complete revascularization and a smaller incidence of perioperative infarction are factors that have contributed to the improved results over the years. Nonetheless, improved patency with the internal mammary artery graft cannot be ignored and may indeed contribute to the favorable evolution of bypass graft operations.

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A-V BLOCK IN PRINZMETAL'S ANGINA

Bharati et al.[1] write that transient atrioventricular (A-V) block during attacks of Prinzmetal's angina has been well documented and that electrocardiograms have suggested an A-V junctional block in all published cases but one, reported by Bodenheimer et al.[2] In our opinion the exception ought not to be considered so. Indeed, in that case the QRS complex during the A-V block was of the supraventricular type and, in the absence of a His bundle recording, it seems logical to suppose that the block occurred at A-V node.

Actually A-V block, when it is related to anginal attacks as in Prinzmetal's angina, always occurs at the A-V junction and cannot occur in the distal portion of the conduction system.[3] This portion has multiple vascularization provided by both the anterior and the posterior descending arteries so that a widespread disturbance of blood supply is necessary for the onset of an A-V block and the conduction defect never occurs without a concurrent extensive septal myocardial infarction. On the contrary, the block during anginal attacks always occurs at the A-V node because this structure is highly sensitive to ischemia[4] and is more vulnerable because it is supplied by a single vessel, the arteria "septi fibrosi." The arteria arises from the vessel that inferiorly crosses the crux cordis and therefore, in Prinzmetal's angina, which is generally associated with active disease of a single coronary artery, A-V block almost constantly appears when angina affects the inferior wall of the heart. This rule[3] that the A-V block in anginal attacks always occurs at A-V node is not invalidated by the rare cases[5] in which the block complicates an angina affecting the anterior wall of the heart. Indeed also in these cases in which an uncommon blood supply of A-V node must be supposed, the QRS complex is of the supraventricular type.

Do Bharati et al. agree with our rule?

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REPLY

There is not enough information reported by Bodenheimer and co-workers concerning the patient in question (Patient 2), to draw a strong conclusion regarding site of A-V block. The patient had ventricular tachycardia and one blocked P wave during an episode of Prinzmetal's angina. Careful scrutiny of the blocked P wave (Fig. 3 of their paper), reveals conducted P waves with a narrow QRS complex before and after the one blocked P wave, with a slight decrease in the P-R interval after the block. This observation is consistent with A-V nodal block. Because of the presence of ventricular arrhythmia, it is also conceivable that the blocked P wave reflected pseudo A-V block secondary to a concealed ventricular ectopic beat.[1,2]

We agree with Fazzini and Marchi that A-V block complicating anginal attacks is usually of A-V nodal origin. However, it is conceivable to us that transient ischemia in the His bundle or trifascicular conduction system, or both, might also produce acute reversible block.[3] The latter occurrence might be more likely in patients with preexistent conduction disease and obstructive coronary disease involving several coronary arteries, so that the ventricular septum with its overlying specialized conduction system might be supplied by only one coronary vessel. Spasm of this vessel could trigger block at a site other than the A-V node.

Our experience in both electrophysiology and pathology makes us very hesitant about formulating rules. Almost as quickly as we formulate new rules, our co-workers in other laboratories (and sometimes we ourselves) find exceptions.

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DOBUTAMINE IN ACUTE MYOCARDIAL INFARCTION

There are two possible errors in the report by Gillespie et al.[1] on dobutamine in patients with myocardial infarction. The first occurs in the Methods section in which one of the criteria for entering the study is "pulmonary arterial occlusive pressure less than 10 mm Hg." This statement is at odds with the statement in the Results section that the treated patients had a "significant decrease in pulmonary arterial occlusive pres-

sure (from 21.5 ± 2.7 to 16.7 ± 1.6 mm Hg)." These two statements are obviously mutually exclusive. The second is the stated criterion of the "cardiac index less than 2.7 liters/min per m^2." In the Results the authors report "a significant increase in cardiac output (from 4.9 ± 0.37 liters/min. . .) before treatment to 6.0 ± 0.38 liters/min. . . ." If the "standard" figure of body surface area of 1.73 m^2 is used, then the mean cardiac index before treatment was 2.83 liters/min per m^2, which is above the range stated as criterion for admission to the study.

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References

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REPLY

The values for pulmonary arterial occlusive pressure and cardiac index should indeed have read "10 mm Hg or more" and "2.7 liters/min or more" rather than "less than" those values. We regret the errors in notation.

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OBESITY AND ISCHEMIC HEART DISEASE

The results of Rabkin et al.[1] leave no doubt that a higher body mass index is significantly associated with development of myocardial infarction, sudden death and coronary insufficiency. However, I find their conclusion that "overweight is a definite risk factor" is not adequately proved by their data.

Definition requires that a risk factor must have a proved causal relation to the disease implied, and it seems to me that this is not fulfilled in the case of obesity and ischemic heart disease. The possibility exists that subjects who start to experience the results of an early and slight coronary atherosclerosis react with self-restriction with regard to physical activity, without admitting this to themselves. It is more than natural that someone who tires more easily than usual and experiences a slight shortness of breath or other indications that "he is not in a good physical shape" will react with a reduced desire for sports and other physical activities and that this response will result in weight gain. Such a sequence of events has not been excluded by Rabkin et al. and therefore, although I fully accept their findings that a greater incidence of ischemic heart disease is found in obese subjects, I would like to add a word of caution to their conclusion that obesity is a "risk factor" in the development of coronary atherosclerosis.

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Reference

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REPLY

The requirement for a causal relation is not part of the definition of a risk factor in general usage:

1. "The coronary risk factors are those abnormalities—demonstrable in persons free of clinical CHD (coronary heart disease)"—known to be *associated* with significantly increased risk of developing the disease in subsequent years."[1]
2. "An attribute which appears to occur more commonly among persons with coronary heart disease than control subjects is defined as a risk factor. It is implied in this particular definition that an association between the disease and a risk factor is not necessarily causal."[2]
3. "The risk factor concept in coronary heart disease (CHD) is based on the finding of statistically significant *associations* between incidence of CHD and values for the variables in question. Studies performed so far have not shown that any of the risk factors are actually causative."[3]
4. "Follow-up studies of persons judged to be free of CHD at entry examination have identified several characteristics *associated* with increased risk of CHD in future years. Age, arterial blood pressure and serum cholesterol concentration uniformly emerge as important risk factors."[4]
5. "Epidemiological studies have shown a significant relationship between the incidence of CHD and various prospective characteristics commonly termed risk factors."[5]

Finding an association is only one step in the proof of causation. We hoped that our finding of an association between body weight and ischemic heart disease would stimulate hypotheses in this field and we are interested to read Stern's. Although we have no evidence to support or refute his hypothesis that early coronary atherosclerosis limits physical activity, which in turn causes an increase in body weight, some comments are in order. The young age of our cohort at entry means that the coronary atherosclerosis would have had to exert its effects when these men were in their *20's* so that they would be overweight at entry. This and the fact that physical inactivity is one of many variables in the equation yielding overweight do not make this hypothesis attractive to us.

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Progress Report

Cardiology developed rapidly in the years immediately after the Second World War as a result of the introduction of cardiac catheterization and echocardiography and the growth of cardiac surgery. These developments underlined the need for international collaboration in communication and in the promotion of advances in cardiology.

The European Society of Cardiology was founded in 1947, and the first World Congress of Cardiology was held in Paris in 1950. The International Society of Cardiology (ISC) was formed at this time with the objects of stimulating development of cardiology in all aspects, improving scientific exchange of information, contributing to the scientific development of its members, the maintenance of ethical standards and organization of courses, conferences and appropriate activities, in addition to sponsoring World Congresses of Cardiology every 4 years. The Asian Pacific Society of Cardiology was formed in 1956.

In 1957 the International Cardiology Foundation was created as a lay organization with medical membership to promote public education in cardiovascular disease and to raise funds for the advancement of cardiology of the world. In 1970 the International Cardiology Federation (ICF) was formed from the Foundation.

In 1970, at the VIth World Congress of Cardiology in London, proposals for a merger between the ISC and ICF were discussed and the principles were agreed upon at the VIIth World Congress of Cardiology in Buenos Aires in 1974. The Assembly of the ISC directed that the details of the merger worked out by a Long Range Planning Committee, to be composed of representatives of both organizations. The merged organization would be essentially a medical scientific body, dedicated to the promotion of world cardiology through the stimulation of research, teaching, lay and professional education and through the encouragement of preventive aspects of cardiology. Fund raising and public relations would be important aspects also. The president would be medically qualified and there would be a preponderance of medically qualified members on the executive board at all times. It was agreed that the merged organization be called the International Society and Federation of Cardiology (ISFC).

Following agreement from national societies and foundations of cardiology the merger was confirmed at the meeting of the Long Range Planning Committee in November 1976. The Assembly of the ICF agreed to dissolve at its meeting in January 1977 on the understanding that the Assembly of the ISC would do likewise at the VIIIth World Congress of Cardiology in 1978. Because of the difference in timing of the Assemblies of the two organizations, the ISFC could not be finally ratified on a permanent basis for a further 20 months, but it would, for practical purposes work entirely as a single organization in order to promote its objectives and, in particular, to encourage and maintain the work of the Scientific Councils and the lay education programs.

The immediate aims of the ISFC are to raise sufficient funds to maintain its programs and the administration necessary to direct and support them and to sponsor and assist in every way possible the activities of the scientific councils and Public Education Committee. These activities cannot be sustained without adequate funds, which must be obtained by subscription from the national societies that are members of the ISFC. In return the ISFC will perform important functions in scientific communication, lay education and the sponsorship of meetings. Examples of programs of lay education and scientific research are the "World Hypertension Year 1978," which is an exercise in public education supported by the World Health Organization, and the multinational collaborative research program on "Congestive Cardiomyopathy" organized by the Scientific Council on Cardiomyopathy.

It is also planned, when funds permit, to create ISFC research and teaching fellowships to enable young cardiologists to engage in research activities and to conduct teaching programs in selected centers in developing and developed countries.

There are seven scientific councils which cover the subjects of arteriosclerosis, ischemic heart disease, cardiomyopathies, epidemiology and prevention, hypertension, pediatric cardiology, rehabilitation and thrombosis and hemostasis.

As the complexity of cardiologic investigations and treatment increases, and as the demands of advancing cardiovascular disease become more insistent, cooperation and integration among international cardiologic organizations become essential. The special relations between the continental societies of cardiology and the International Society and Federation of Cardiology are being defined and stabilized at present so that further collaboration in teaching and research activities and the organization of conferences will become possible.

The bulletins of the ISC and ICF have been combined in the journal *Heartbeat,* which will give news of the national societies and foundations of cardiology, dates of meetings and reports of the scientific councils and public education events. Details of international meetings will be given regularly; in particular, information about the VIIIth World Congress of Cardiology in Tokyo in 1978 and "World Hypertension Year 1978" will appear from time to time.

The year of the merger, 1977, has heralded a new era in international cardiology, and the active support and encouragement of cardiac societies and foundations all over the world will be appreciated as an essential requirement for success.

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International Society and
Federation of Cardiology

Acknowledgment

I am much indebted to Dr. Vittorio Puddu, past president of the ISC, for data on the history of that organization and to Madame Marianne de Figueiredo for material on the history of the ICF.

AMERICAN COLLEGE OF CARDIOLOGY NEWS

The following individuals were elected to membership in the American College of Cardiology on December 1, 1977 in the category indicated.

FELLOWSHIP

BACHE, Robert J., MD, Minneapolis, MN
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LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education.

Each continuing education program is directed toward a specific target group including: adult cardiologists (CD), internists (IM), pediatric cardiologists (PDC), and family practitioners (FP). For additional information concerning the programs listed below or for a complete schedule of programs through October 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

APRIL THROUGH JUNE 1978

Apr. 3–6 **Cardiac Emergencies: Recognition and Therapy (CD) (IM).** Charles E. Rackley, MD, FACC, director

Apr. 10–12 & 13–15 **Adult Echocardiography: Clinical Applications and Recent Advances (CD) (IM).** Pravin M. Shah, MD, FACC, director

Apr. 17–20 **Pediatric Echocardiography (PDC).** Richard A. Meyer, MD, FACC, director

Apr. 24–26 **Exercise Testing: Diagnostic and Physiologic Considerations (CD) (IM).** Keith Cohn, MD, FACC, director

May 8–10 & 22–24 **Electrocardiography of Arrhythmias (CD) (IM).** Charles Fisch, MD, FACC, director

May 15–18 **Update in Cardiology (CD).** R. Joe Noble, MD, FACC, director

May 31–June 2 **Diagnosis & Management of Clinically Important Arrhythmias (FP) (GP) (IM).** William P. Nelson, MD, FACC, director

June 19–22 **Congestive Heart Failure: A Changing Scene (CD) (IM).** Charles B. Mullins, MD, FACC, director

June 12–14 & October 23–25 **Update in Cardiology (CD) (IM).** Douglas P. Zipes, MD, FACC

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

MARCH 1978 THROUGH AUGUST 1978

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

MAR. 3–4 — **Complex Problems in Congenital Heart Disease.** Robert M. Sade, FACC and Arno R. Hohn, FACC, co-directors. Kiawah Island Inn, Charleston, SC

MAR. 6–9 — **Twenty-seventh Annual Scientific Session.** Dean T. Mason, FACC, president. Anaheim Convention Center and Disneyland Hotel, Anaheim, CA

MAR. 10–11 — **Post Anaheim, California. Symposium on Clinical Cardiology.** Anthony N. DeMaria, FACC, director. Kauai Surf Hotel, Kauai, HI

MAR. 27–31 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

MAR. 30–APR. 1 — **Contemporary Management of Acute Myocardial Infarction by the Family Physician.** Robert S. Eliot, Chairman and Ernie J. Chaney, Alan D. Forker, Harold Kalman and Thomas Nicholas, program committee. Sarasota Hyatt House, Sarasota, FL

APR. 3–7 — **Consultant's Course in Cardiology.** Michael V. Herman, FACC, director and Simon Dack, FACC, Richard Gorlin, FACC and Louis E. Teicholz, FACC, co-directors. Mount Sinai Medical Center, New York, NY

APR. 3–12 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 12–14 — **Vectorcardiography: A Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 19–21 — **Echocardiographic Solutions to Clinical Cardiovascular Problems.** Joseph K. Perloff, FACC and John S. Child, FACC, directors. Century Plaza Hotel, Los Angeles, CA

MAY 8–10 — **The Physiologic Basis for Diagnosis and Treatment of Heart Disease—A Tribute to William Harvey on his 400th Birthday (1578–1657).** J. Willis Hurst, FACC, director and Robert C. Schlant, FACC, co-director. Colony Square Hotel, Atlanta, GA

MAY 12–14 — **Rational Drug Therapy in Ischemic Heart Disease.** Robert J. Lee, director, Palmer House, Chicago, IL

MAY 12–15 — **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

MAY 18–20 — **Cardiovascular Nuclear Medicine and Comparative Techniques: 1978.** Lawrence S. Cohen, FACC, Alexander Gottschalk, Barry L. Zaret, FACC, directors. Yale University School of Medicine, New Haven, CT

JUNE 15–17 — **Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** Arthur D. Hagan, FACC, director and Walter V. R. Vieweg, FACC and Joel S. Karliner, FACC, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

Aug. 26–28 — **Tutorials in the Tetons: Cardiac Emergencies (Fourth Annual).** Robert S. Eliot, FACC, director and Alan D. Forker, FACC, William P. Nelson, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

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Edwin L. Rothfeld, South Orange, New Jersey
Abraham M. Rudolph, San Francisco, California
David C. Sabiston, Jr., Durham, North Carolina
Antone Salel, Solana Beach, California
Arthur A. Sasahara, West Newton, Massachusetts
Steven Scheidt, New York, New York
Benjamin J. Scherlag, Miami, Florida
Gerold L. Schiebler, Gainesville, Florida
Clyde D. Schoenfeld, Pittsburgh, Pennsylvania
David Schwartz, Cincinnati, Ohio
Mark Schwartz, New York, New York
Bernard L. Segal, Philadelphia, Pennsylvania
Pravin M. Shah, Rochester, New York
William C. Sheldon, Cleveland, Ohio
Libi Sherf, Tel Hashomer, Israel
Mark Silverman, Atlanta, Georgia
Toby L. Simon, Bethesda, Maryland
Laurence J. Sloss, Boston, Massachusetts
Maurice Sokolow, San Francisco, California
Edgar Sowton, London, England
Frank C. Spencer, New York, New York
Albert Starr, Portland, Oregon
Elliott Stein, Newark, New Jersey
Paul D. Stein, Detroit, Michigan
Barry Stimmel, New York, New York
Edward S. Stinson, Stanford, California
H. William Strauss, Boston, Massachusetts
Ralph M. Sussman, New York, New York
H. J. C. Swan, Los Angeles, California
Abdul J. Tajik, Rochester, Minnesota
Morton E. Tavel, Indianapolis, Indiana
Salvador Treves, Boston, Massachusetts
Richard Van Praagh, Boston, Massachusetts
John H. K. Vogel, Santa Barbara, California
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Albert L. Waldo, Birmingham, Alabama
Max Harry Weil, Los Angeles, California
Sylvan Lee Weinberg, Dayton, Ohio
Arthur C. Weisenseel, Jr., New York, New York
Vernon E. Wendt, Grand Rapids, Michigan
E. D. Wigle, Toronto, Ontario, Canada
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G. Wilner, Evanston, Illinois
Nathaniel Wisch, New York, New York
George B. Wisoff, New Hyde Park, New York
Steven M. Wittenberg, Springfield, Massachusetts
Steven Wolfson, New Haven, Connecticut
Dennison Young, Bronx, New York
Eliot Young, Boston, Massachusetts
Paul N. Yu, Rochester, New York
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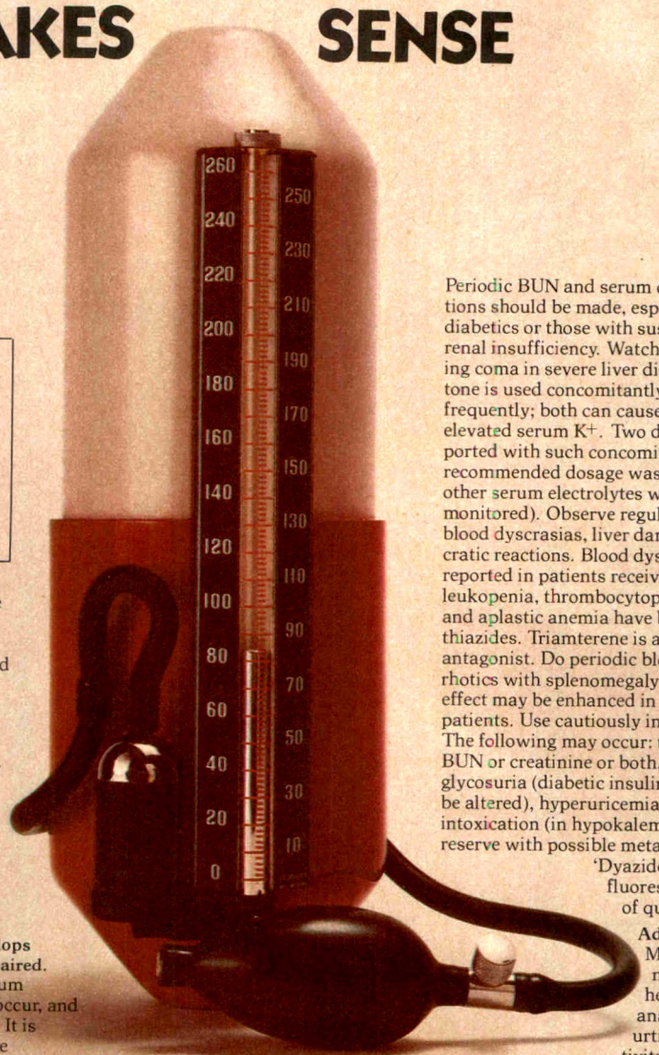
TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

MAKES SENSE



Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

FOR LONG-TERM CONTROL OF HYPERTENSION.* SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY. (SEE WARNINGS SECTION.)

SK&F CO., Carolina, P.R. 00630

SK&F CO.
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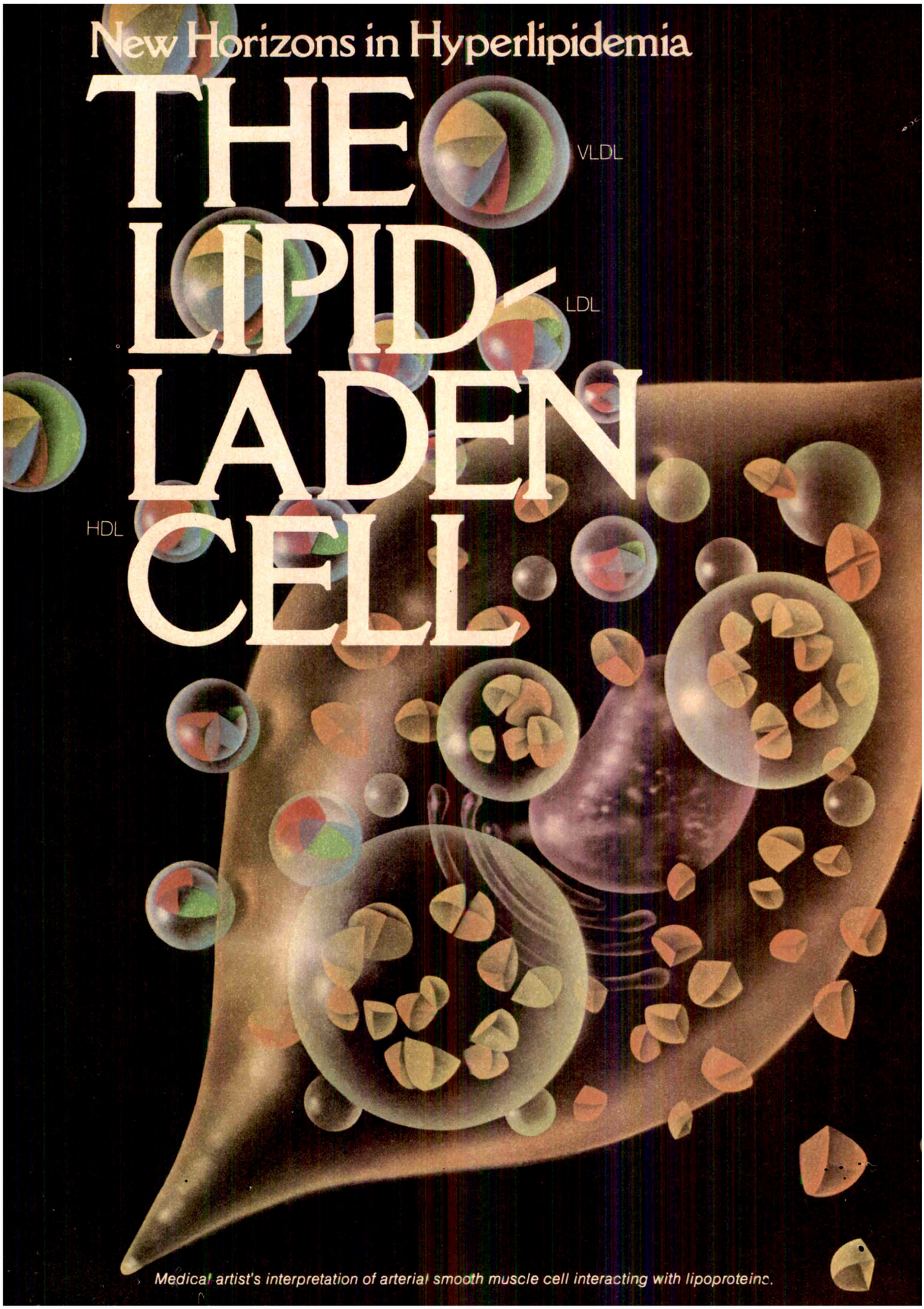
New Horizons in Hyperlipidemia

THE LIPID-LADEN CELL



Medical artist's interpretation of arterial smooth muscle cell interacting with lipoproteins.

Lipid overloading in the arterial smooth muscle cell: proposed biochemical mechanisms

The process by which a normal arterial smooth muscle cell is transformed into a lipid-laden "foam" cell is highly complex and, as yet, not completely understood. But from the findings of an ever-increasing number of animal and human studies,[1-28] investigators have begun to piece together a theoretical picture of what may occur—a picture that adds important new perspectives to an understanding of hyperlipidemia.

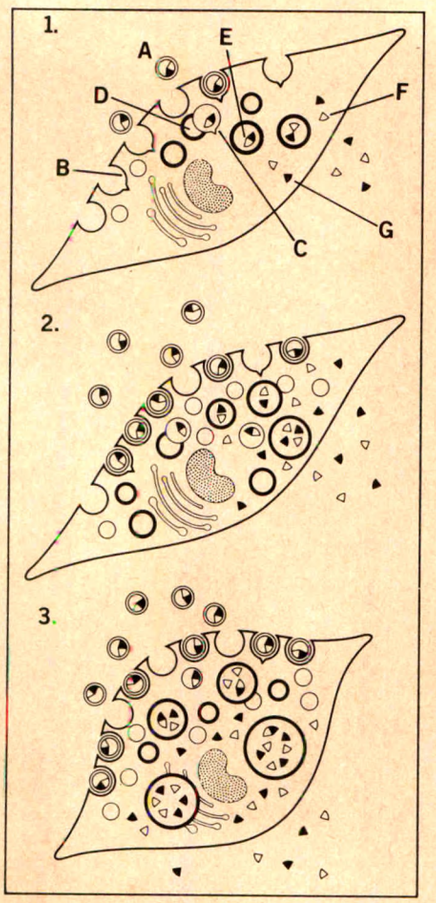
What emerges from this research is that induced and/or genetic abnormalities in the metabolism of arterial smooth muscle cells may be crucial to their evolution into a lipid-laden form.[6,9,11,19] Specifically, there appear to be alterations in the ability of these cells to bind, internalize and degrade triglyceride-rich very low density lipoproteins (VLDL) and cholesterol-rich low density lipoproteins (LDL).[1,2]

The endothelium, which normally acts as a selective barrier[20,25] to the entry of plasma constituents into the arterial wall, also appears to influence the behavior of arterial smooth muscle cells.[23,26] As a result of injury to the endothelium and/or increased concentrations of circulating lipoproteins, excessive quantities of lipids may breech the endothelial barrier, and accumulate in smooth muscle cells.[1,2,5,20,23] Eventually, the cells die and rupture, releasing their lipid content into the extracellular matrix of the arterial wall.

Human tissue cultures yield new insights into an insidious progression

Theories postulating the sequence of events that may produce lipid-laden cells were originally based on observations in a variety of animal species. Now, through the application of dramatic new biochemical techniques, many of these theories are finding support in studies of human cells. It is now possible to culture human arterial smooth muscle cells from explants of tissue obtained during vascular surgery,[1-3,10,18] human fibroblasts taken from the skin,[6,8,12,14] and human endothelial cells derived from umbilical veins.[15-17] Methods for studying the interaction of these cells with lipoproteins in culture have permitted the assessment of lipoprotein binding, uptake, and degradation.[1,2] (See diagrams at right). While this *in vitro* data requires *in vivo* confirmation, it can serve as a useful basis for investigation and discovery with regard to the relationship between plasma lipids and lipid accumulations in arterial walls.

The evolution of a lipid-laden cell: a working hypothesis[24] Disturbances in the normal metabolism of arterial smooth muscle cells can lead to marked changes in the lipid content of the arterial wall. The most notable change is an increase in cholesterol esters, but there are also increases in the concentration of other lipids, including triglycerides.[20] Following is a highly simplified outline of a working hypothesis to explain lipid overloading, as it relates primarily to LDL:[24]



1. *The arterial smooth muscle cell's natural defenses against lipid overload*[6-8,12] Given an artery with the endothelium intact, and a low level of circulating plasma lipoproteins, LDL uptake is predominantly of the high affinity, receptor-dependent type: LDL molecules (A) are bound to receptor sites (B) on the endothelial surface, internalized via pinocytotic vesicles (C), fused with lysosomes (D) which hydrolyze the cholesterol ester (E) component of the lipoprotein into its basic constituents, free cholesterol (F) and fatty acid (G). The free cholesterol triggers compensatory mechanisms which decrease cholesterol synthesis by the cell and also reduce the number of its LDL receptors, thereby helping to limit further entry of LDL. Under normal conditions, this acts to protect the arterial smooth muscle against lipid overload.

2. *The cell's response to an increased metabolic load.* Injury or disruption of the endothelium and/or a substantial increase in circulating plasma lipoproteins leads to entry of larger amounts of LDL and other lipid substances into the cells. At these higher plasma levels, lipids appear to be taken up predominantly via a low affinity, nonreceptor-mediated process.[7] Endocytosis is greatly stimulated and the number and size of the lysosomes increase in an effort to keep up with the increased load.[21]

3. *The cell's lipid-regulating mechanism overwhelmed.* If the state of increased metabolic activity needed to handle the extra lipid load persists, the "finely-tuned" regulatory mechanism may break down. With lipid passage into the cell virtually unchecked, massive intracellular accumulations of cholesterol and other lipids ensue. As a result, cellular function may be compromised, leading to cell death and deposition of lipids in the extracellular space.

High levels of circulating lipoproteins: a key factor in cellular overload

In human tissue cultures, arterial smooth muscle cells take up substantial quantities of VLDL and LDL and relatively small amounts of HDL.[1,2] This contrasts with the low uptake of VLDL and high uptake of HDL observed in smooth muscle cells of certain animal species (e.g., rats)[2] which have no propensity for lipid overloading in arterial cells.

Cellular concentrations of lipids also bear a relation to lipid concentrations in the serum. For example, both human and calf endothelial cells in tissue culture evidenced significantly higher levels of triglycerides and fatty acids after exposure to hypertriglyceridemic serum than did controls subjected to medium containing normal serum.[17]

These provocative studies have exciting implications for further investigation. *However, it must be remembered that there is to date no proof that lowering serum lipoprotein concentrations in humans will prevent or reverse the processes that produce lipid-laden cells.*

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Note: Schematic illustrations of cells adapted from Wolinsky, H.: Cardiovasc. Med. *1*:41 (Sept.) 1976.

New Horizons in Hyperlipidemia

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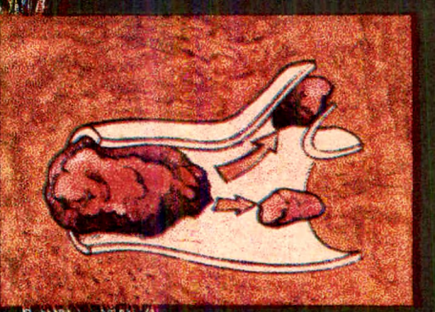
3715.

THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

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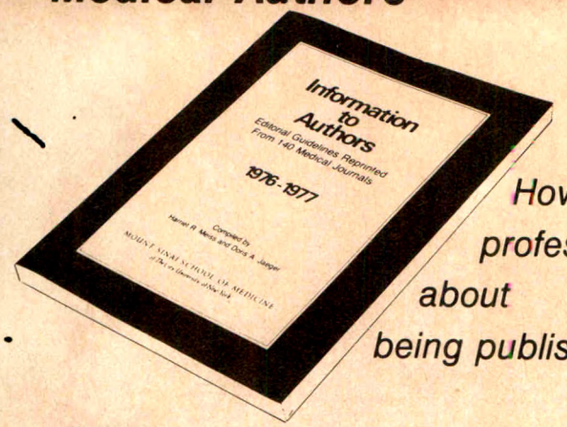

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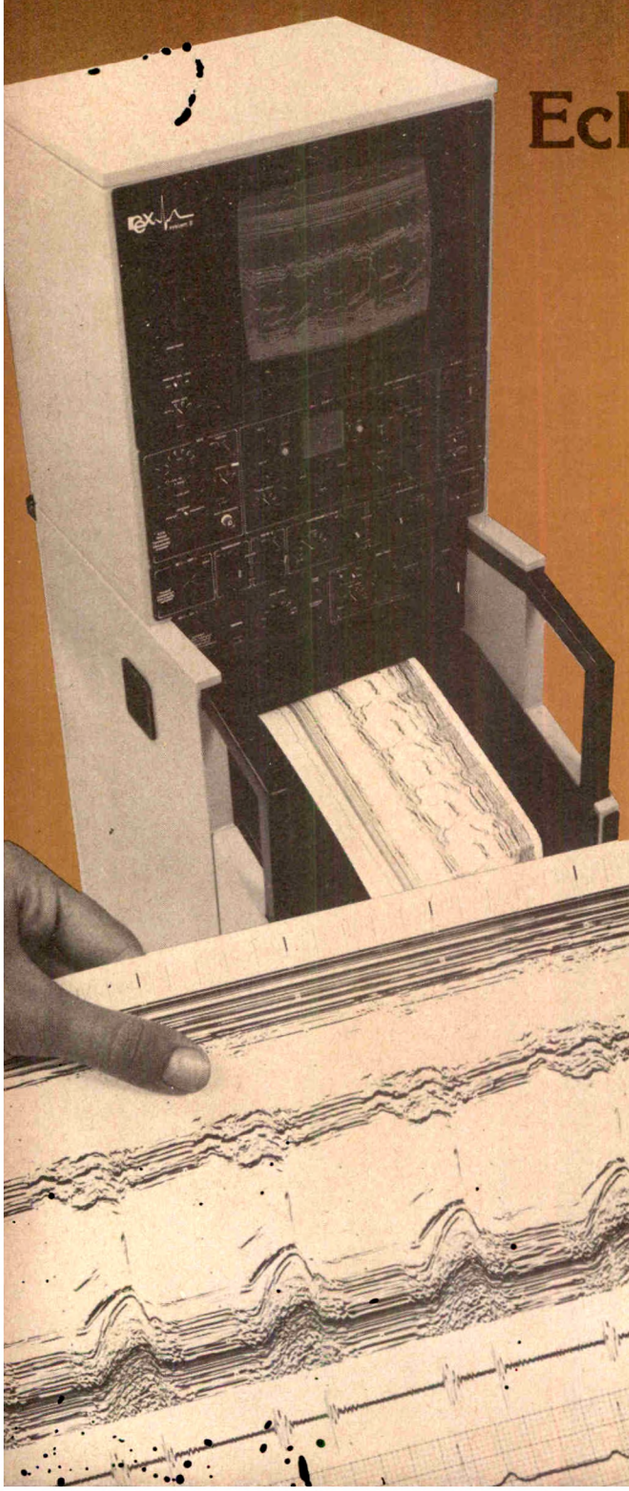

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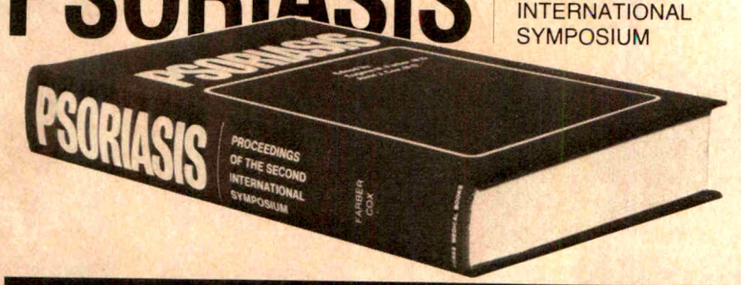

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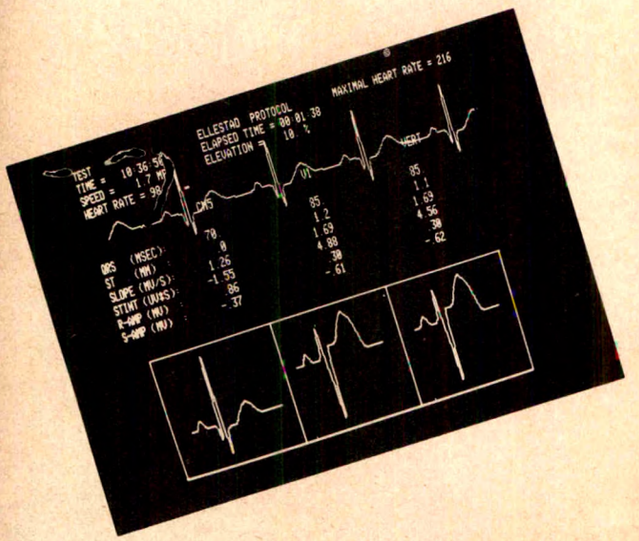

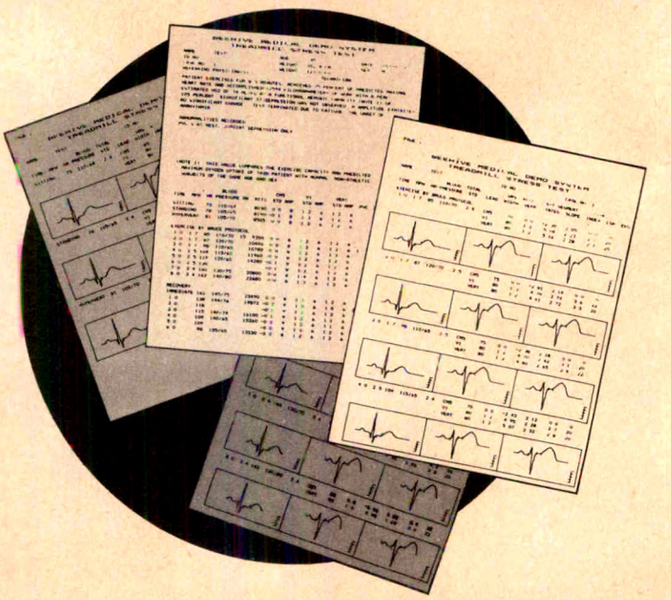

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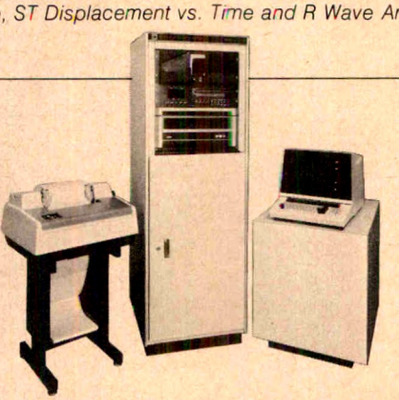

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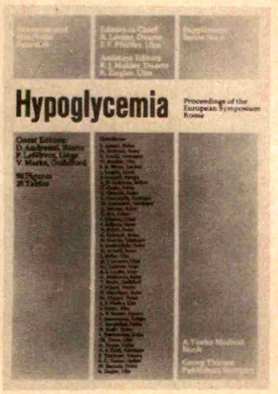

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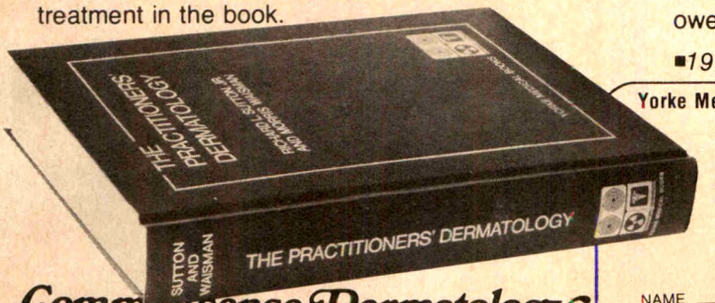

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- effective in all grades of hypertension
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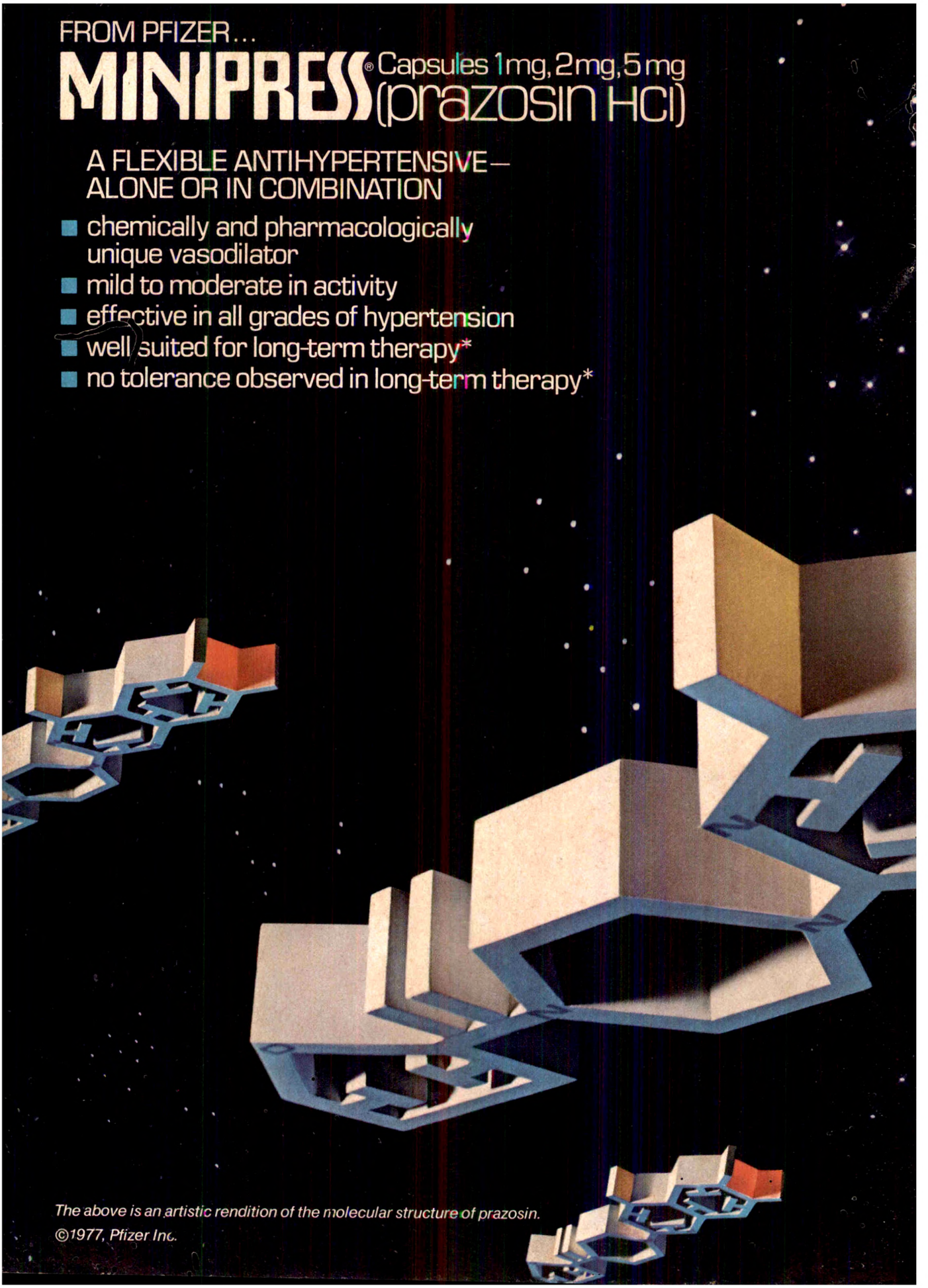

The above is an artistic rendition of the molecular structure of prazosin.

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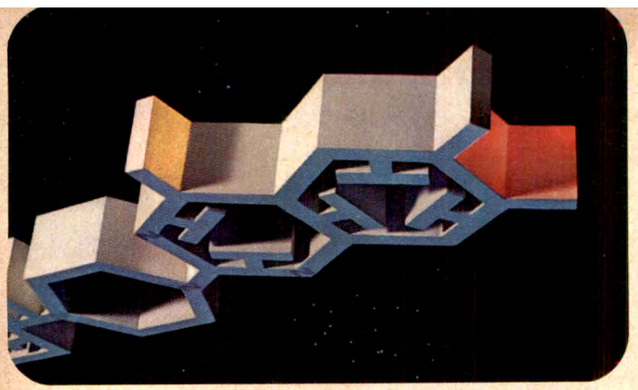
*Minipress has been studied in patients on continuous therapy for periods of up to 5 years.

Before prescribing Minipress, WARNINGS and
DOSAGE AND ADMINISTRATION sections should be carefully reviewed.

Please see Brief Summary on last page for indications, warnings and adverse reactions



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- Direct action on the arterioles without clinically significant effects on cardiac output, renal blood flow or glomerular filtration rate. Reflex tachycardia frequently associated with other vasodilators is much less common with Minipress.
- No tolerance observed in long-term therapy in patients on continuous therapy for periods of up to 5 years.
- Studies in patients on continuous therapy for periods of up to 5 years indicate that Minipress is well suited for long-term therapy.
- Side effects most frequently experienced with Minipress in a series of 934 patients were: dizziness (10.3%), headache (7.8%), drowsiness (7.6%), lack of energy (6.9%), weakness (6.5%), palpitations (5.3%), and nausea (4.9%). A small percentage of patients have experienced orthostatic hypotension (3.4%) and syncope (1.3%). (For a more detailed description of orthostatic hypotension and syncope, see Warnings in Brief Summary before initiating therapy with Minipress.)
- Starting dosage: 1 mg t.i.d.
- Usual maximum recommended dosage: 20 mg daily, given in divided doses.
- Some patients can be maintained adequately on a b.i.d. dosage regimen.
- Available in 1-mg, 2-mg, and 5-mg capsules.

AJ16

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit dose packages of 100 (10 x 10's).

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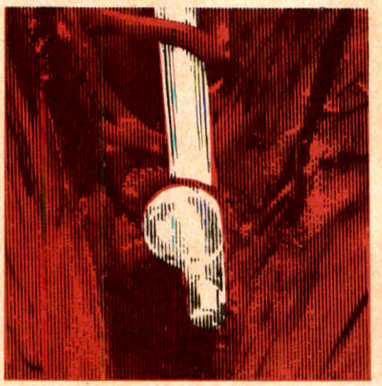

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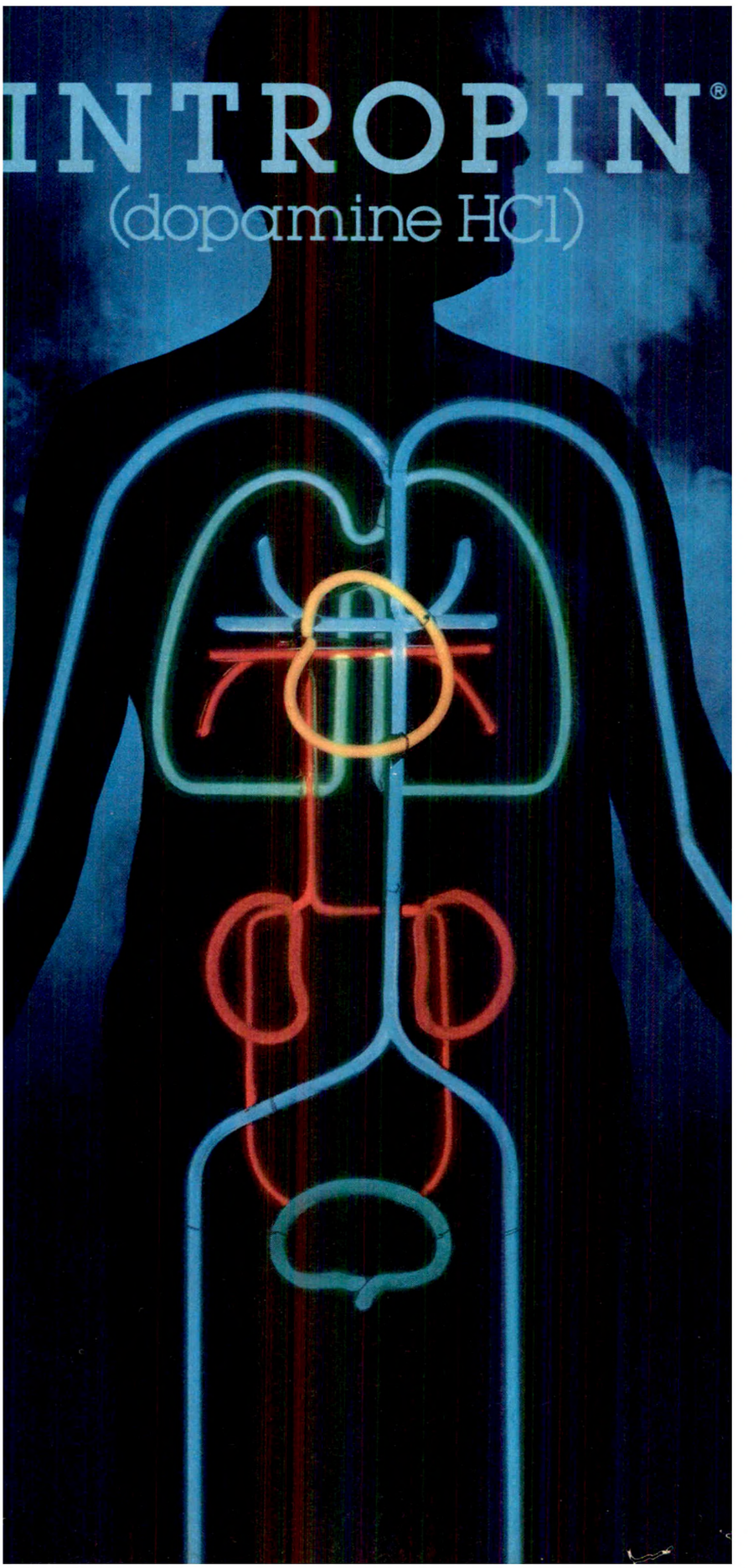
INTROPIN®
(dopamine HCl)

In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

Maintains kidney function

The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

ARNAR-STONE LABORATORIES, INC.
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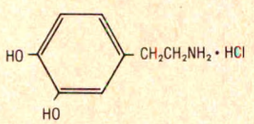
INTROPIN® (dopamine HCl)

(See last page of this advertisement for full prescribing information.)

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts a positive inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs — Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output — Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension — Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy — Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children — The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia — Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure — If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation — INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease — Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT — Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics — Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required — Close monitoring of the following indices — urine flow, cardiac output and blood pressure — during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution — Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration — INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

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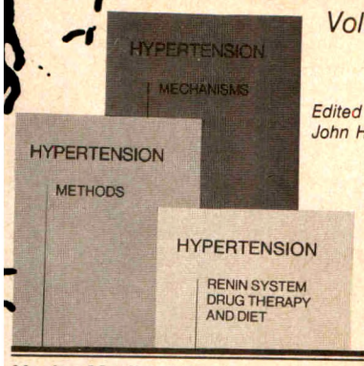

Edited by
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Master Professor of Medicine
Director of the Cardiovascular Center
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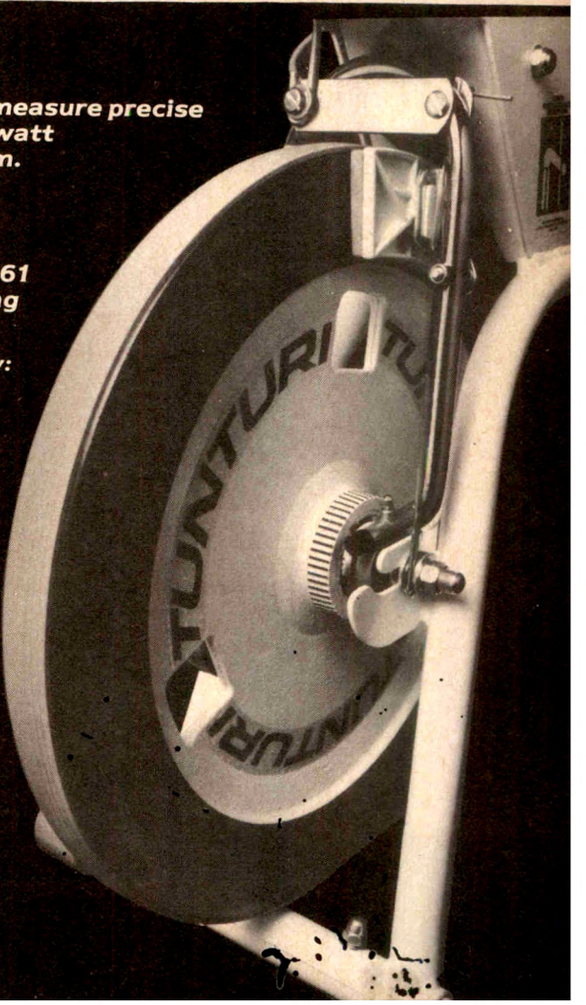

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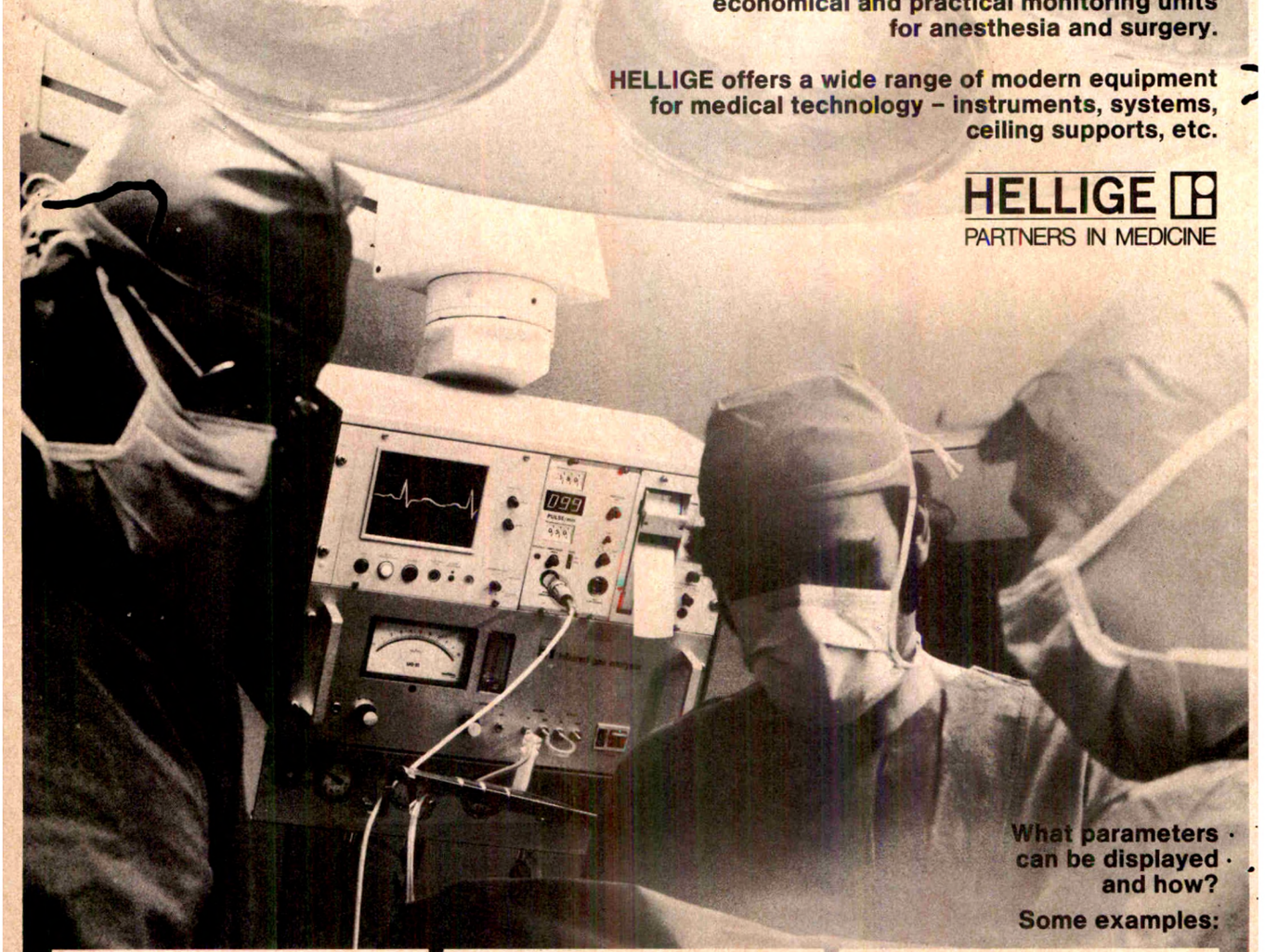

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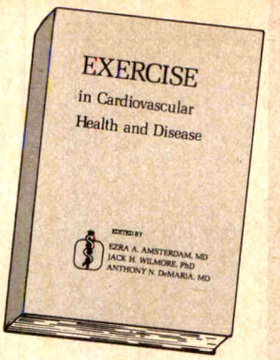

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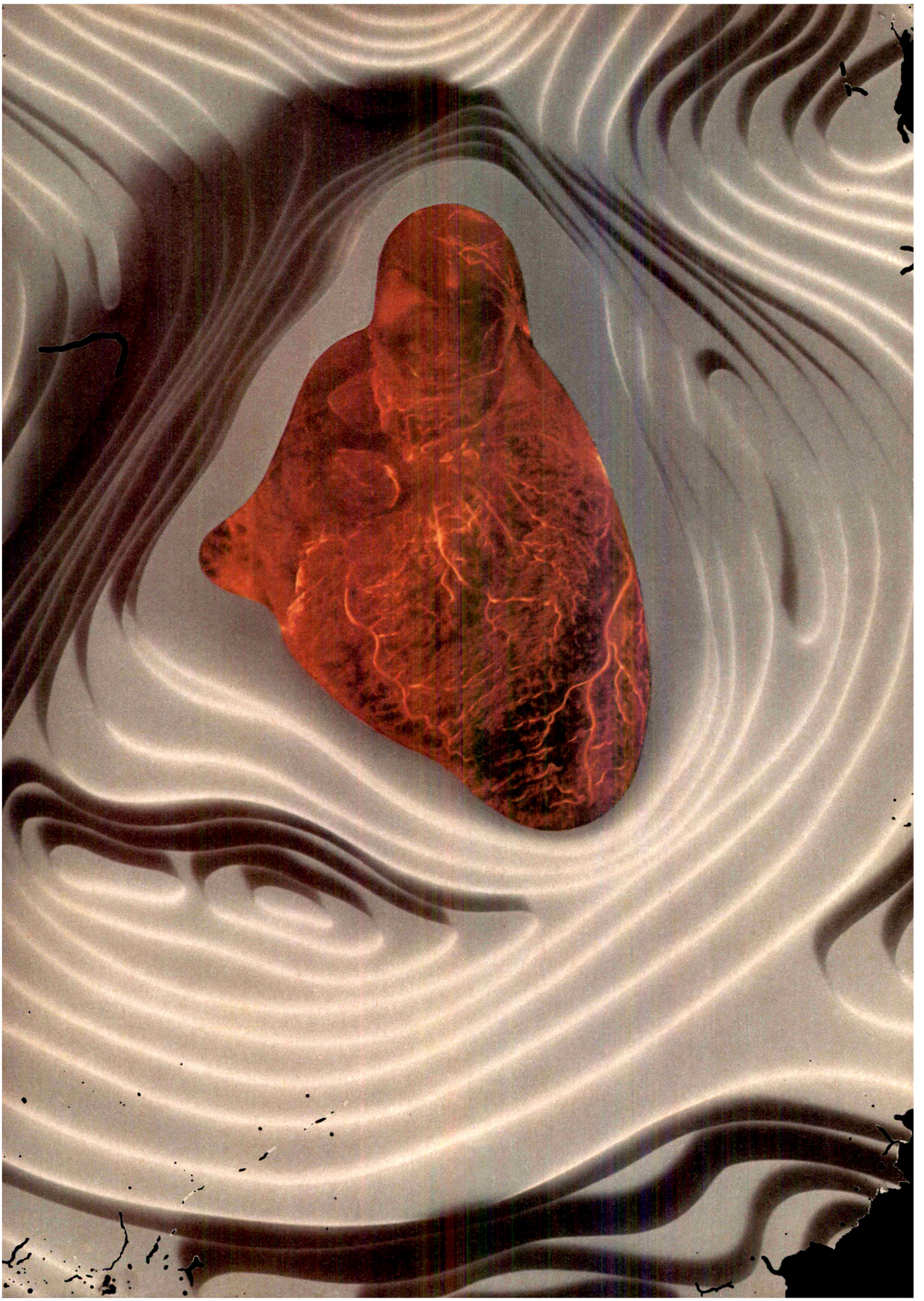
24. LONG-TERM PHYSIOLOGIC ADAPTATIONS TO EXERCISE WITH SPECIAL REFERENCE TO PERFORMANCE AND CARDIORESPIRATORY FUNCTION IN HEALTH AND DISEASE — *William C. Adams, PhD; Malcolm M. McHenry, MD; Edmund M. Bernauer, PhD*
25. PHYSICAL ACTIVITY FOLLOWING MYOCARDIAL INFARCTION — *William L. Haskell, PhD*
26. CARDIAC REHABILITATION: PRINCIPLES, TECHNIQUES AND APPLICATIONS — *John Naughton, MD*



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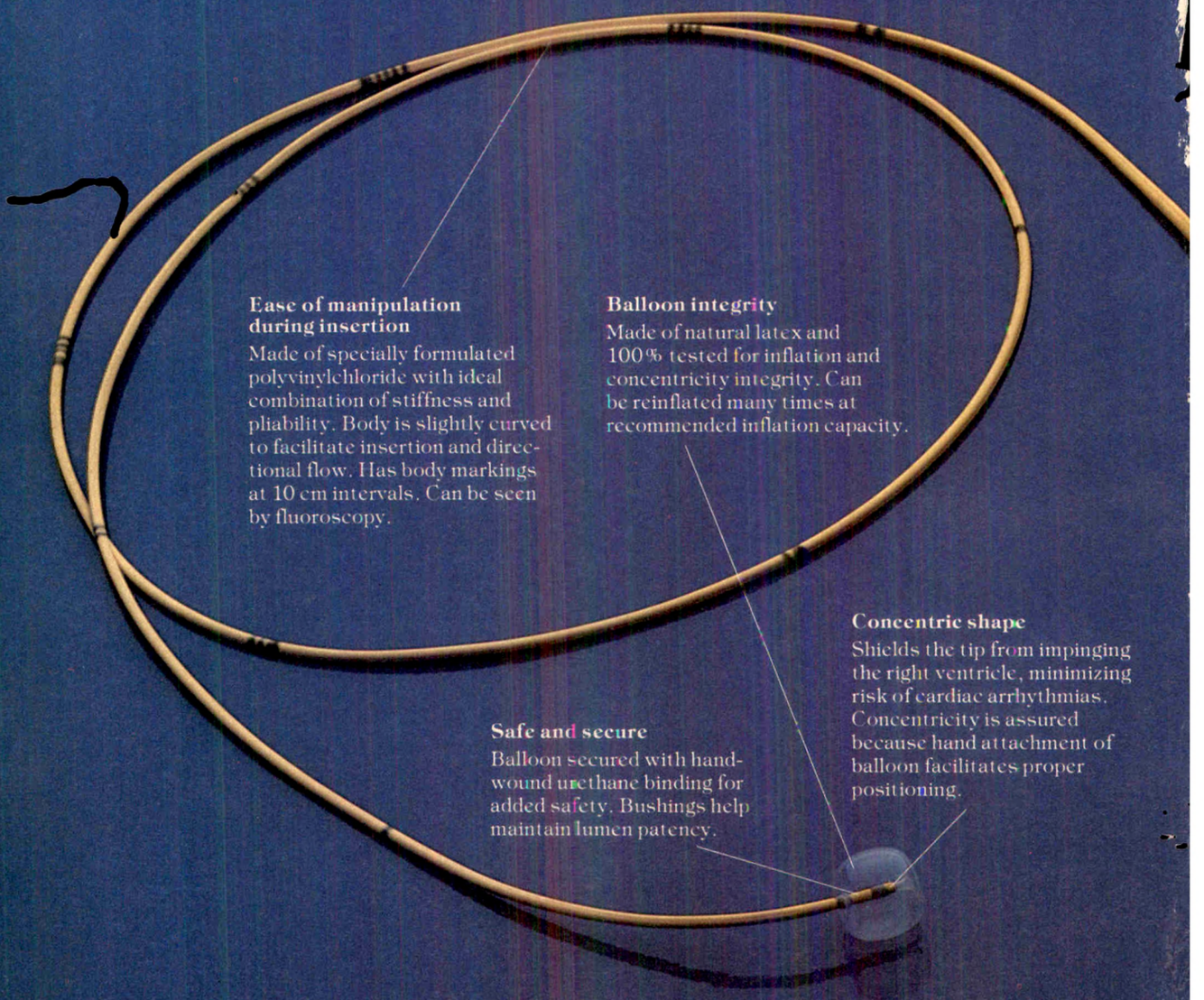

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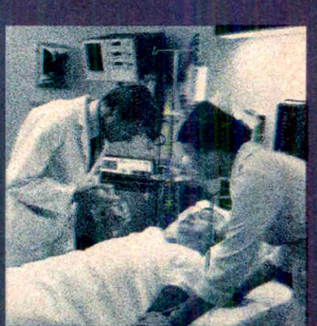

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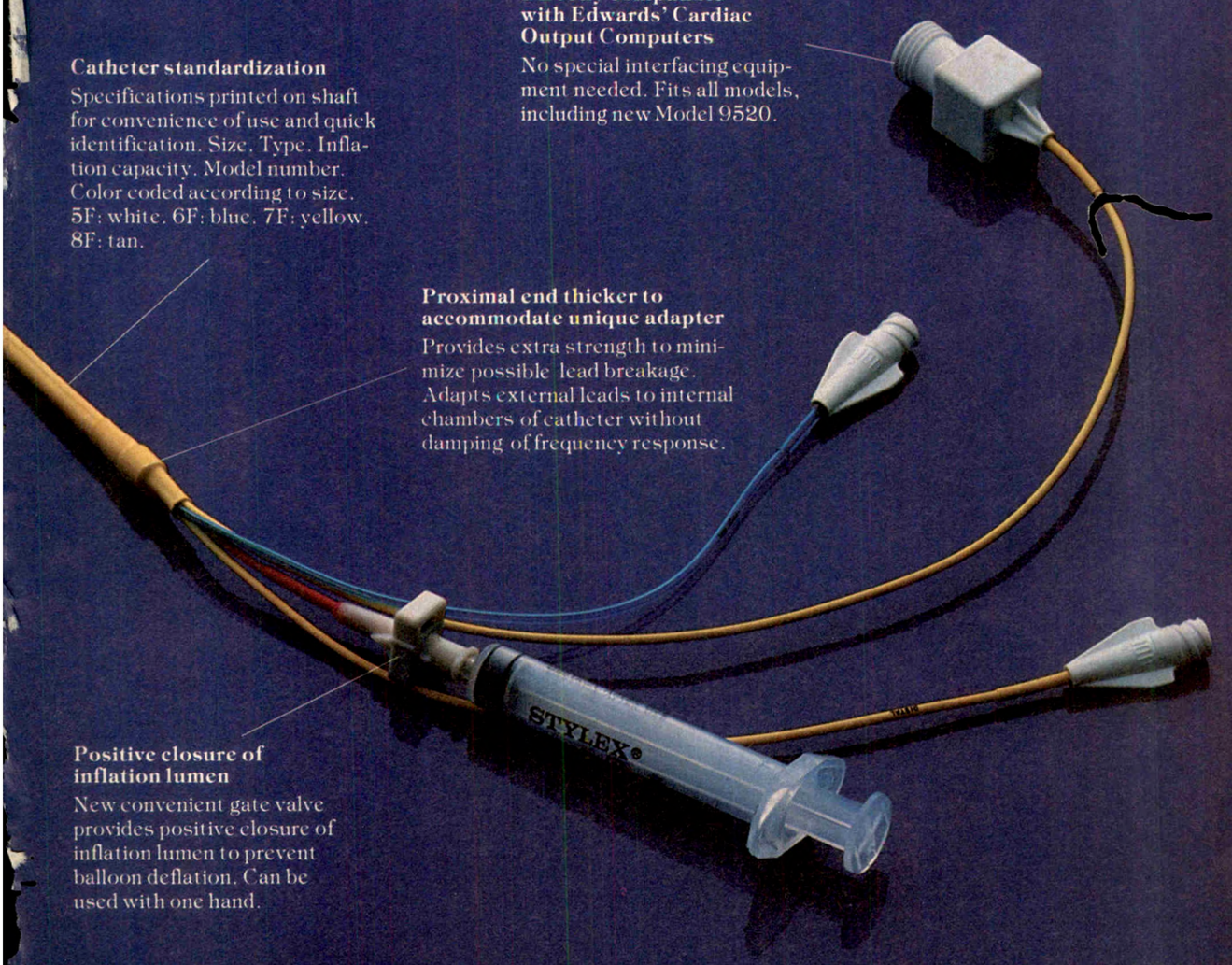

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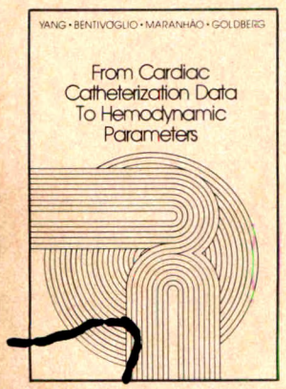

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Reflecting both advances in knowledge and refinements in techniques, this revised and expanded edition provides a practical way to convert data from the cardiac catheterization laboratory into relevant hemodynamic parameters for the assessment of cardiac function. From the simplest readings to the most complex calculations, instructions are so complete that no other reference is needed for their practical application. The book is equally useful for physicians performing catheterization and those who must interpret the data.

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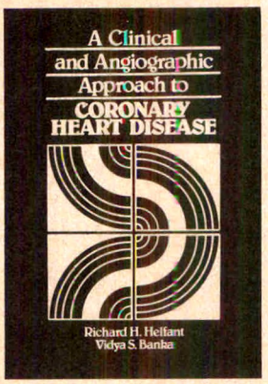

A CLINICAL AND ANGIOGRAPHIC APPROACH TO CORONARY HEART DISEASE.

By **Richard H. Helfant, MD,** Chief, Division of Cardiology and Associate Professor, Presbyterian-University of Pennsylvania Medical Center; and **Vidya S. Banka, MD,** Director, Cardiac Catheterization Laboratory and Assistant Professor of Medicine, Presbyterian-University of Pennsylvania Medical Center

"This text is an excellent correlative study which interrelates the findings on coronary visualization with the clinical expressions of coronary heart disease," says William Likoff, MD. Unlike other texts on angiography, this book evaluates patients with coronary heart disease, not as a homogeneous group, but as subsets characterized by their clinical presentations, laboratory findings, ECG and stress tests, as well as the underlying anatomy and physiology. The authors have masterfully and concisely correlated clinical and angiographic findings to make prognostic and therapeutic decisions, including the indications for surgical procedures, particularly bypass surgery.

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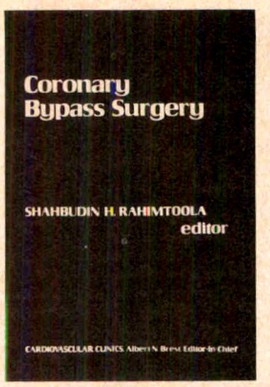

CORONARY BYPASS SURGERY. CARDIOVASCULAR CLINICS SERIES. Volume 8, Number 2

Guest Editor, **Shahbudin H. Rahimtoola, MD, FRCP,** Professor of Medicine, Division of Cardiology, University of Oregon Health Sciences Center, Portland, Oregon

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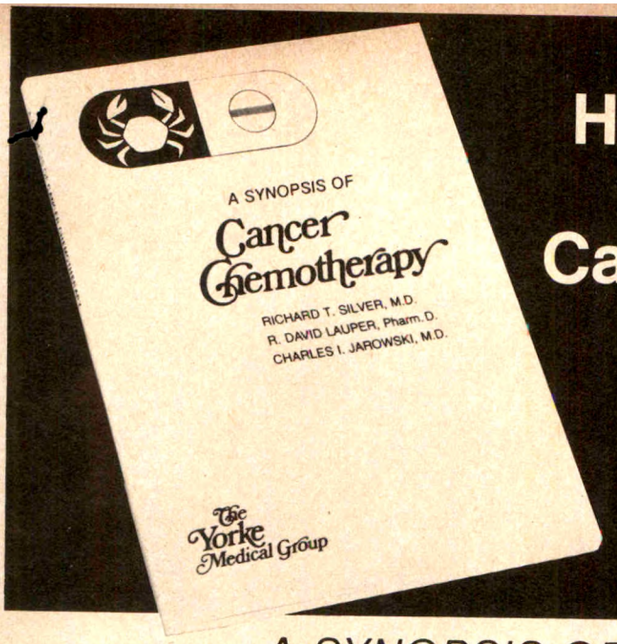

How to Keep Up with the New Drugs in Cancer Chemotherapy

Three authorities from a leading medical center show you how to use the most current chemotherapeutic agents

A SYNOPSIS OF Cancer Chemotherapy

RICHARD T. SILVER, MD, F.A.C.P., F.A.B.C.O.
Chief, Oncology Service, Div. Hematology-Oncology, Clinical Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Exec. Officer, Cancer & Leukemia Group B.

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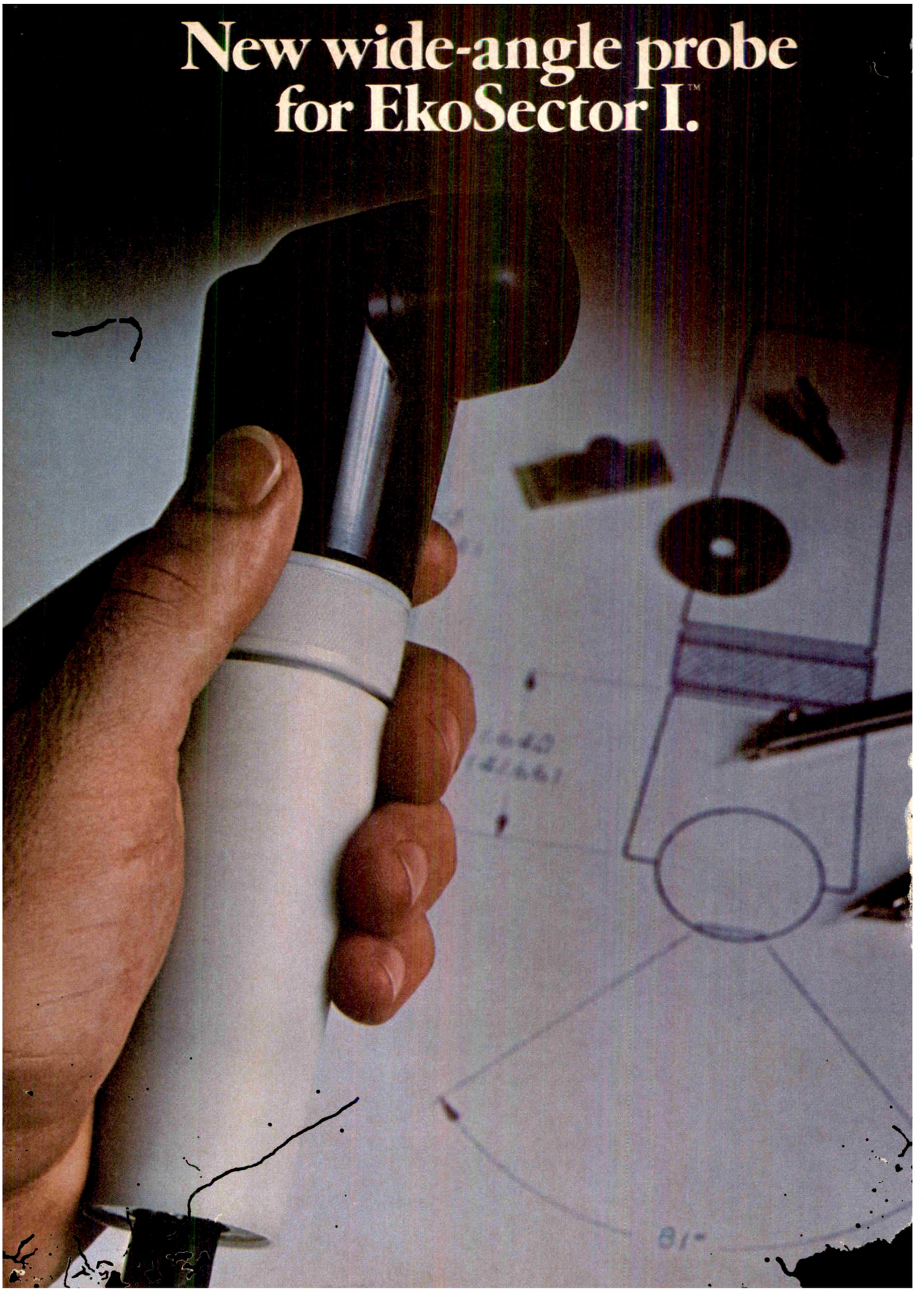

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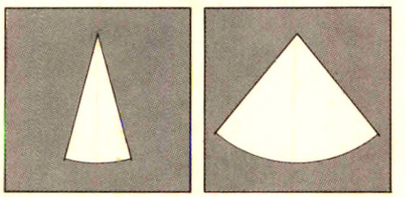

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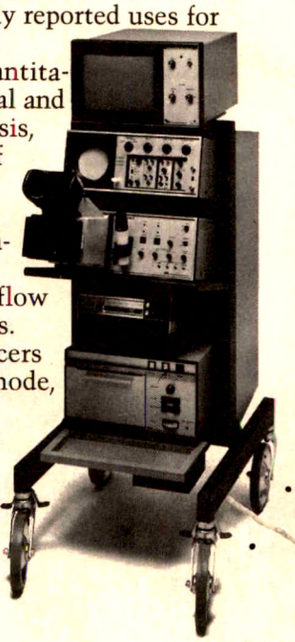

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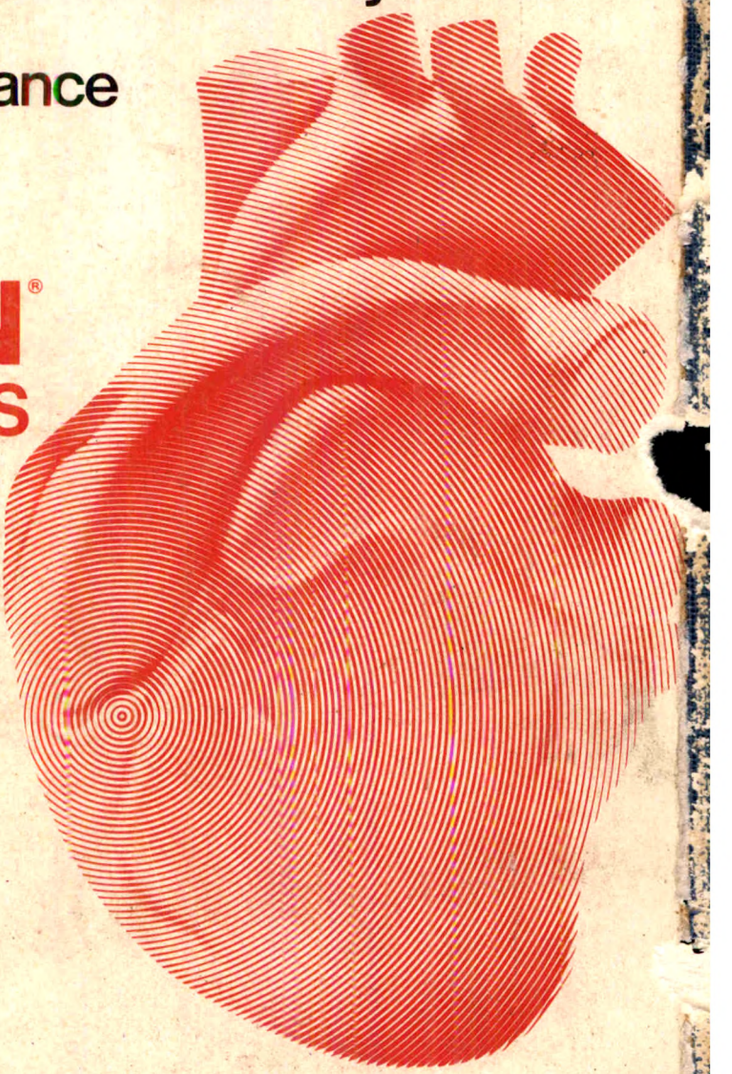

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